THE PHYSICIAN'S GUIDE

TO

CHEMOTHERAPY

THE PHYSICIAN'S GUIDE TO CHEMOTHERAPY

BY

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PREFACE

In writing this book I have been guided by the needs of doctors in family practice and in hospital for up-to-date information on the clinical uses of antibiotics. The book is intended primarily as a work to which the physician can refer easily for guidance in treatment, and by describing the antibiotics themselves, to give him a deeper understanding of the basic problems of chemotherapy.

I include features which may seem to be inconsistent with these aims or to fall outside the scope of the book For instance, diseases are mentioned which the general practitioner would not attempt to treat, but it is felt that their omission would make this account of chemotherapy incomplete and detract from the value of the book as a whole. For the same reason I include brief descriptions of the treatment of some of the more rare infections and of those encountered only in other parts of the world Treatment by means other than chemotherapy is not described, except when it directly influences chemotherapy itself.

Throughout I have laid emphasis on bacteriology, because antibiotic therapy is founded and depends for its success upon knowledge of the infecting micro-organism. Bacteriological diagnosis is an important and often indispensable aid to treatment in practice and, as it is made in most diseases by examination of the urine, fæces, blood or inflammatory exudates, it is within the reach of every physician.

The nomenclature proposed in Topley and Wilson's "Principles of Bacteriology and Immunity" (Third Edition, 1946) has been adopted because it is widely accepted in this country and most closely resembles that in common use. Nevertheless, I also give the colloquial name when it differs so much from the accepted name that its identity might not be recognised.

The word "antibiotic" is freely used in its widest sense as a noun to denote all agents whose action is antibiotic, and thus it includes synthetic products in addition to those prepared from [illegible]

clarity of each section to the reader who is in search of information on some particular subject.

The bibliography has been selected with the principal object of providing the interested reader with more comprehensive reviews of matters which have passed beyond the stage of research and have been assessed with reasonable certainty. In the case of current research and clinical trials and those aspects of chemotherapy of which I have little or no personal experience, original articles are quoted.

P. N. S.

Farnborough, Kent,
1952.

ACKNOWLEDGEMENTS

I HAVE pleasure in acknowledging and at the same time thanking my colleagues for their invaluable assistance in preparing and writing this book.

Dr. Duncan Leys and Dr. George Brownlee have at all times been willing to discuss the innumerable problems which have arisen and to offer helpful criticism on points of detail. Dr. George Brownlee has also given particular help in the sections on the pharmacology of the antibiotics.

I am indebted to Dr. K. O. Rawlings, who has generously read and corrected the proofs, and to Dr J. S. Ebsworth, who has suggested many improvements in the text from the point of view of the general practitioner.

In preparing the sections on the use of antibiotics in clinical medicine and surgery, I have received much assistance and advice from Mr. C C. Cookson (Surgical Infections), Dr W. S L Gilchrist (Cardiovascular Diseases), Mr. H. S. Gild (Infections of the Upper Respiratory Tract), Dr V E Lloyd (Venereal Diseases), Dr. D. G. Madigan (Tuberculosis), Dr. E J. Moynahan (Infections of the Skin), Mr. D. P van Meurs (Infections of the Eye) and Dr S D V Weller (Infections of Childhood)

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INTRODUCTION

For the past fifteen years the treatment of disease caused by specific micro-organisms has been dominated by advances made in the field of experimental chemotherapy. Progress has been so rapid and the application of new knowledge to prophylaxis and [illegible]

clinical aspects is enormous, inclusion in a practical guide of too much pharmacological detail might obscure those characteristics which determine clinical value. Pharmacology, which governs the clinical use of chemotherapeutic substances, will therefore be described *separately from practical details of treatment.* When two or more drugs are known to be effective and a choice has to be made, the reasons for placing them in order of preference are g [illegible]
chlo [illegible]
some [illegible]
exactness nor recommend a final régime of treatment.

If these new drugs are to be used to the best advantage, it is important that the physician possess the background knowledge upon which *understanding of their properties and limitations* is based Besides obtaining better results, the physician will be in a more favourable position to avoid the unpleasant and, occasionally, dangerous toxic manifestations which some of these drugs may produce.

The Place of Chemotherapy in Treatment

Specific antibacterial and antiviral substances are playing an increasingly important part in the treatment of infective diseases. Most causal pathogens are susceptible, *to a greater or less extent,*

to one or more of the chemotherapeutic agents. Their dramatic efficiency in controlling certain infections has led to their taking the principal rôle in treatment. Attention has been focused on this success to such an extent that it is often assumed that the administration of a chemotherapeutic drug is all that is required. Their new success indeed often obscures the fact that their sole action is

Chemotherapy of acute infections characterised by exotoxin formation, such as diphtheria, tetanus and other clostridial infec-

of treatment.

In diseases such as typhoid fever, endotoxin is released when the micro-organism dies. Hence the massive destruction of bacteria by effective chemotherapy may cause a rapid increase in the *severity of the disease, which at the best is transient*, but at the worst may be overwhelming and prove fatal to a patient whose resources are already strained to the utmost. Although this demonstrates their great antibacterial power, it also serves to show that there are risks in applying these substances too suddenly when there is no means of neutralising the released endotoxins. To *avoid this, a therapeutic régime with a low initial* dosage has been recommended in typhoid fever, with the object of spreading the release of endotoxins over a longer period of time.

In the absence of chemotherapy the host is capable of bringing

effective phagocytosis and lysis which are the processes respon-
for the final disposal of pathogens. However intrinsically potent the agent employed, a favourable response cannot be expected if the cellular defences are weak or impaired. Among the conditions which depress the cellular defences are debility from prolonged ill-health, malnutrition, and large abscesses requiring surgical drainage. In certain tissues—*e.g.*, meninges and cartilage—the cellular reaction to infection is always relatively weak.

In chronic infections stalemate is usually reached where the patient is able to contain and limit but not eradicate the invading organisms; it is then also found that the response to chemotherapy

is poor. For example, acute brucellosis may be rapidly cured whereas in chronic brucellosis treatment is frequently unsuccessful.

The reaction of the body's defences in infancy and old age is poor and often inadequate, even against comparatively non-pathogenic bacteria. On this account, at the extremes of life, chemotherapy may be unsuccessful in acute infections, an example is the high mortality of pneumonia in these age groups, in spite of adequate therapy.

The antibody response of the host is a relatively slow process and plays little part in the immediate reaction to acute infection. Antibody-antigen reactions require the presence of the organism for a considerable period, and it is conceivable that by too prompt and complete elimination of minor infections the stimulus to man's defensive mechanisms may be insufficient to maintain his immunity at an efficient level. If carried beyond a certain point, this might outweigh the benefit to be derived from chemotherapy For instance, it is unwise to treat every streptococcal sore throat as a routine with sulphonamides or penicillin For the same reason there are numerous infections, transient and usually mild, encountered in practice which are best treated by symptomatic methods only.

The secondary effects of infection may be prevented by timely chemotherapy, but are unaffected if they have become established; such effects are the presence of devitalised tissue, cellular and bacterial débris, thrombosis, circulatory and renal failure, or intoxication by metabolic products. The host may be capable of correcting these conditions if they are of limited severity, but often it will be necessary to employ other equally specific treatment such as surgery or transfusion These pathological disturbances of structure and function are, more often than failure of chemotherapy to eradicate the micro-organism, causes of unsuccessful treatment.

Any patient who does not respond satisfactorily to treatment should be thoroughly examined and investigated to detect secondary effects which may accompany the particular infection

Just as infection may be the cause of pathological conditions which themsel[illegible] treatment, so pathological states may [illegible]

tion. Until the underlying pathology has been corrected the danger of relapse will remain. Chemotherapy then takes its place, often an essential one, in an ordered plan of treatment with full utilisation

of any other measures that can assist the patient in overc
the pathogen and its effects. The aim of the physician in
scheme of treatment, whether specific therapy is employed
is to weight the struggle in favour of the host by augm
his resources and weakening those of the invader. In every
tion the patient is to be aided by applying the principles o
nursing, and symptomatic treatment by drugs, local applic
etc. Equally important are the correction of dehydration, th
vision of a suitable and appetising diet and the ensuring of
sleep and peaceful mind.

THE SIGNIFICANCE OF ANTIBIOTIC ACTION

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of toxins, throw an extra strain on the patient. This was esp
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enzyme reactions which, under therapeutic conditions,
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test. Fortunately, in the usual infections, this theoretical poss
is far outweighed by the antibiotics' therapeutic value.

CHOICE OF

In ideal circumstances the
agent rests primarily upon exact b.

in mixed infections, includes co-existent micro-organisms. Often, however, the physician has to choose and prescribe an antibiotic on the evidence of clinical diagnosis, from which the causal organism may be presumed. Initial measurement of the pathogen's sensitivity to the range of available drugs, which may vary from strain to strain, is of practical value and assumes great importance in severe and resistant infections; this information must be

POTENCY

Other things being equal, the most potent agent should be chosen. In fulminating infections, especially when no effective alternative is available, the urgency of securing the greatest possible therapeutic effect may require that the risk of toxic effects be taken, the danger of the drug being outweighed by the danger of the disease.

RANGE OF ACTIVITY

In infections by mixed pathogenic flora an antibiotic of wide

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satisfy the requirements of both potency and range of activity.

RESISTANCE

The frequent development of acquired resistance to an antibiotic is a grave drawback to its use. Often it may be possible to use an alternative without undue loss of potency, but if this is not possible, every device, including combined therapy, should be used to delay the emergence of resistant strains. In general, a strain which has become resistant to one antibiotic retains its original sensitivity to other agents.

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The Significance of Antibiotic Action

Antibiotics, quite apart from their toxic manifestations or release of toxins, throw an extra strain on the patient. This was especially noticeable with the earlier sulphonamide derivatives, but is not so marked in the later preparations. In the case of penicillin it appears to be virtually absent, but the possibility must always be kept in mind with new drugs and antibiotics.

The principle of use of antibiotics is competition with the pathogen for a common metabolite which may also be necessary to man.[1] Successful chemotherapy implies that the competition between antibiotic and pathogen has deprived the latter of a metabolite necessary for its life or growth. In the process man's metabolic system may be affected, throwing an extra strain on his

[illegible]

enzyme reactions which, under therapeutic conditions, brings about the death of the organism. This effect is more readily obtained against susceptible organisms than against the host. Upon this margin is based the therapeutic index of the drug and the degree of safety in clinical use. An interesting current example is provided by aureomycin and chloramphenicol. It has been shown that they inhibit the growth not only of the organism but also of fœtal cells.[2] Whether this will prove to be a factor in depressing cellular reaction and repair in man has not yet been put to the test. Fortunately, in the usual infections, this theoretical possibility is far outweighed by the antibiotics' therapeutic value.

Choice of Drug

In ideal circumstances the choice of a specific antibacterial agent rests primarily upon exact bacteriological diagnosis, which,

strain to strain, is of practical value and assumes great importance in severe and resistant infections; this information must be weighed against knowledge of their proven efficiency in the human disease. Potency, range of activity, toxicity and the incidence of emergent resistant strains must also be taken into consideration.

POTENCY

Other things being equal, the most potent agent should be chosen. In fulminating infections, especially when no effective alternative is available, the urgency of securing the greatest possible therapeutic effect may require that the risk of toxic effects be taken, the danger of the drug being outweighed by the danger of the disease.

RANGE OF ACTIVITY

In infections by mixed pathogenic flora an antibiotic of wide range should be chosen. Similarly, when an exact bacteriological diagnosis is impossible, or when, as in bronchopneumonias of infancy and old age, it is difficult to label any particular micro-organism as causative, the antibiotic with the widest range against Gram-positive bacteria offers the best chance of success. When potency must be sacrificed with loss of therapeutic effect it is preferable to employ a combination of drugs which together satisfy the requirements of both potency and range of activity.

RESISTANCE

The frequent development of acquired resistance to an antibiotic is a grave drawback to its use. Often it may be possible to use an alternative without undue loss of potency, but if this is not possible, every device, including combined therapy, should be used to delay the emergence of resistant strains. In general, a strain which has become resistant to one antibiotic retains its original sensitivity to other agents. The emergence of resistant strains is becoming of wide epidemiological significance as well as being an immediate cause of therapeutic failure. The consequence may already be seen in the high incidence of sulphonamide-resistant gonococcal infections, the increasing number (more than

5 per cent.) of staphylococcal infections insensitive to penicillin and also of strains of *Myc. tuberculosis* insensitive to streptomycin.

The immediate and delayed effects of acquired resistance are thus of great importance and are fully discussed later.

Toxicity

Toxicity may be broadly divided, according to the cause, into—

1. *Specific drug toxicity (e.g., the effect of streptomycin on the* 8th nerve).
2. Toxicity from impurities (*e.g.*, fever).
3. Acquired hypersensitivity (*e.g.*, drug rashes).
4. The patient's "idiosyncrasy" (*e.g.*, agranulocytosis).
5. Side effects (*e.g.*, sulphonamide crystalluria).

Mild toxic reactions are generally no contraindication to the use of an antibiotic. Severe reactions, if not preventable by careful management, prohibit further use of the drugs except in a severe illness when no alternative is available.

[illegible]

be impossible to ensure an alkaline urine as an aid to solubility. These are factors which greatly increase the risk of sulphonamide toxicity.

Cost and convenience are matters of small importance when a severe infection has to be treated, but in family practice and particularly in milder infections the physician rightly must [illegible] and toxic reactions, [illegible] ld [illegible] ce.

Methods of Administration

The route chosen for administration is dictated by the need [illegible] of infection. [illegible] and [illegible] the pharmacological properties of individual antibiotics the subject is considered in greater detail.

Full advantage should be taken of the fact that higher local drug concentrations can be obtained by injection into the place of infection—*e.g*, pleural cavity, spinal theca, joint cavities—than can be obtained by systemic administration

Some drugs, among which are many of the sulphonamides, aureomycin and chloramphenicol, are so acid, so alkaline or so insoluble that severe local inflammation limits the routes by which they may be administered.

A hazard of injection is that of introducing insensitive organisms at the site of injection—*e g., Bact. coli* with penicillin injections or resistant *Staph. aureus* with streptomycin injections. Scrupulous attention to asepsis is the surest method of prevention.

The Nature of Resistance

The susceptibility of a micro-organism to specific antibacterial agents depends on the possession of a cellular enzyme system which the drug can disrupt Several such enzyme systems are recognised, and it has been shown that antibiotic substances act on different systems and in different ways The end result is interference with cellular metabolism causing inhibition of growth and multiplication, or actual death of the cells and lysis. In the first instance, especially, the defence mechanisms of the host are required to complete the eradication of the organism from the body and to bring about clinical cure.

A resistant micro-organism may not possess an enzyme system

destroys penicillin and is thus immune to its action. A few sulphonamide-resistant strains have been shown to synthesise increased amounts of para-aminobenzoic acid, which protects and maintains their metabolic pathways intact. With a few exceptions it has not been possible to demonstrate experimentally any corresponding alteration of metabolism in other instances of acquired resistance. It is presumed that one mechanism by which

would be expected that subsequent bacterial generations would revert to their original method of metabolism which would be manifest as a return of drug sensitivity This does not occur in

practice. Resistance having once developed becomes an inheritable [illegible]

mutants are present. These few cells are capable of multiplying in spite of the presence of the drug, so that soon they become the dominant strain.[3] Similar observations have been made with other organisms and other drugs. Consequently, it is reasonably certain that the few highly resistant mutants present in a colony otherwise sensitive are the origin of resistant strains which may emerge during treatment. It follows that strains of the pathogen which have emerged in the presence of optimal blood concentrations of, for instance, streptomycin will prove totally resistant to optimal blood concentrations of streptomycin.

It also follows that the essential requirement necessary to enable [illegible]

depends on complete and prompt eradication of the organism. In practice this is achieved by bringing an adequate concentration [illegible] reatment. [illegible] les, which [illegible] bacterial multiplication more readily allow resistant strains to become dominant than do bactericidal antibiotics such as polymyxin.

In addition to the immediate effect of acquired resistance on the response of the disease to treatment, the physician may be faced with variations of bacterial sensitivity at the start of treatment. These variations between strains of the same pathogen may be natur [illegible] previous occasi [illegible] insusc [illegible] cocci [illegible] isms to streptomycin.

SIGNIFICANCE OF RESISTANCE IN THERAPY

[illegible] f infections exact bacteriological diagnosis [illegible]

encountered. If the organism is only partially sensitive the concentration of the drug in the blood, cerebro-spinal fluid or urine should

also be estimated. On the basis of this information, dosage may be adjusted to bring about the optimal concentration

After the use of chemotherapeutic substances a small number of viable organisms may persist irrespective of dosage or duration of treatment, and on investigation, can be shown to be of normal drug sensitivity and might be expected to be susceptible. They are entirely distinct from the resistant mutants already described. Their inaccessibility to the drug may be a cause, but cannot satisfactorily explain their persistence in all cases

[illegible]

tissues have become sterile, the causal organism may still be [illegible]

discontinue treatment before the latter is also apparent throws on the patient an extra responsibility, increasing the risks of incomplete success and relapse.

Thus there are several ways in which the pathogen may survive a course of antibiotic therapy. The surviving micro-organisms may, by reason of the mechanisms already outlined, show an increase of resistance. This has two results; the first is to render the drug ineffective in subsequent treatment of the same infection or of relapses, and the second is to cause resistant infections in contact cases.

Fortunately the development of acquired resistance to one drug does not imply acquired resistance to other drugs For example, staphylococci resistant to penicillin remain sensitive to aureomycin, tubercle bacilli resistant to streptomycin remain sensitive to [illegible]

practice. Resistance having once developed becomes an inheritable characteristic and persists in subsequent generations.

In colonies of *H. influenzæ* which are sensitive to low concentrations of streptomycin, a very small number of resistant bacterial mutants are present. These few cells are capable of multiplying in spite of the presence of the drug, so that soon they become the dominant strain.[3] Similar observations have been made with other organisms and other drugs. Consequently, it is reasonably certain that the few highly resistant mutants present in a colony otherwise [illegible]

instance, streptomycin will prove totally resistant to optimal blood concentrations of streptomycin.

It also follows that the essential requirement necessary to enable resistant strains to emerge is that there should be living organisms which survive exposure to the drug. If all organisms have been killed, the emergence of resistant strains becomes an impossibility. *The avoidance of acquired resistance, then, in chemotherapy* depends on complete and prompt eradication of the organism. In practice this is achieved by bringing an adequate concentration [illegible]

multiplication more readily allow resistant strains to become dominant than do bactericidal antibiotics such as polymyxin.

In addition to the immediate effect of acquired resistance on the response of the disease to treatment, the physician may be faced with variations of bacterial sensitivity at the start of treatment. These variations between strains of the same pathogen may be naturally occurring or due to exposure to the drug on a previous occasion. The principal organisms which give rise to relatively insusceptible strains are gonococci to sulphonamides, staphylococci to penicillin and virtually all streptomycin-sensitive organisms to streptomycin.

SIGNIFICANCE OF RESISTANCE IN THERAPY

In the management of infections exact bacteriological diagnosis and estimation of sensitivity now assumes great importance, owing to the increasing frequency with which *resistant strains are* encountered. If the organism is only partially sensitive the concentration of the drug in the blood, cerebro-spinal fluid or urine should

also be estimated. On the basis of this information, dosage may be adjusted to bring about the optimal concentration

After the use of chemotherapeutic substances a small number of viable organisms may persist irrespective of dosage or duration of treatment, and on investigation, can be shown to be of normal drug sensitivity and might be expected to be susceptible They are entirely distinct from the resistant mutants already described. Their inaccessibility to the drug may be a cause, but cannot satisfactorily explain their persistence in all cases.

It is well recognised that certain antibiotic substances, notably streptomycin and sulphonamides, are less effective in the presence of large numbers of organisms or of pus These conditions are [illegible]

tissues have become sterile, the causal organism may still be demonstrable on stained films though it fails to grow on culture. This is well illustrated during the treatment of *H influenzæ* meningitis and is probably due to the host's inability to dispose of the organisms by phagocytosis and lysis as rapidly as they are killed. It is a feature of chemotherapy that disappearance of the organism usually precedes objective clinical improvement Yet to discontinue treatment before the latter is also apparent throws on the patient an extra responsibility, increasing the risks of incomplete success and relapse.

Thus there are several ways in which the pathogen may survive a course of antibiotic therapy The surviving micro-organisms may, by reason of the mechanisms already outlined, show an increase of resistance. This has two results, the first is to render the drug ineffective in subsequent treatment of the same infection or of relapses, and the second is to cause resistant infections in contact cases.

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[illegible]

inhibiting multiplication of the streptomycin-resistant members of the colony, prevents their emergence as the dominant strain. Furthermore, it has been demonstrated that certain drugs in combination are synergistic; their efficacy, when given together, exceeds the sum of their separate effects. If, on the grounds of clinical experience or bacteriological data, it is anticipated that [illegible]

[illegible]

organism.

Whenever there is an opportunity, advantage should be taken of the fact that higher levels of the drug can be obtained at the site of the infection by local (*i.e.*, intrapleural, intrathecal, etc.) rather than by systemic administration. If there is doubt about the possibility of obtaining therapeutic concentrations at the site of *the infection, local administration assumes greater importance.*

As far as antibiotic therapy itself is concerned the risks of failure owing to the persistence of the causal organism, either sensitive or resistant, may be minimised by ensuring a full dosage for a sufficient period of time, reinforced where necessary by local application or by employing a combination of drugs.

Conclusion

The Object of Treatment

The object of treatment, which is to secure clinical cure of the patient, may be achieved by influencing various operative factors to his advantage.

1. Sustaining Host Resistance

The following points are of importance:

(*a*) Rest, both physical and mental.
(*b*) Diet, adequate with regard to calories, vitamins, proteins.
(*c*) Fluids, to correct dehydration.
(*d*) Correction of disturbances of the electrolyte balance.
(*e*) Early detection of abnormal blood conditions (*e.g.*, [illegible])
(*f*) [illegible]
(*g*) [illegible] metabolic disturbances.

2. Eradication of the Causal Organism

(*a*) Specific antibacterial measures (chemotherapy)
(*b*) Non-specific antibacterial measures (*e.g.* surgery).
(*c*) Neutralisation of toxins (antitoxins).

THE CAUSES OF FAILURE OF CHEMOTHERAPY

1. Insufficiency of the Host's Defences

(*a*) Malnutrition.
(*b*) Prolonged ill-health or toxæmia.
(*c*) Chronic infection.
(*d*) *Infancy and old age.*
(*e*) The presence of an undrained abscess.
(*f*) Leucopenia and agranulocytosis.
(*g*) Infection in tissues that do not permit effective cellular reaction to infection, usually on account of avascularity—*e.g.*, varicose ulcers, chondritis, meningitis, etc.

2. Associated Pathological Conditions

(*a*) Predisposing anatomical abnormalities either congenital or the result of previous disease
(*b*) Predisposing metabolic disturbances such as diabetes, avitaminosis, etc
(*c*) Secondary anatomical changes—*e g.*, fibrosis, metaplasia of epithelium.
(*d*) Thrombosis, either from endarteritis or venous stasis.
(*e*) Electrolyte imbalance.
(*f*) Dehydration.

3 Incomplete Bacteriostasis

A. *Initially sensitive and partially sensitive micro-organisms.*

I. Inadequate drug concentration at the site of infection.
(*a*) Too low or too infrequent dosage.
(*b*) Inaccessibility to the drug, and this may be due to—
(i) The site of infection. Drugs vary in their capacity to traverse certain anatomical barriers—*e g.*, streptomycin, penicillin and polymyxin fail to reach the cerebro-spinal fluid in therapeutic quantities when injected into muscle.
(ii) A barrier of devitalised tissue or inflammatory exudate.

concentrations when sulphonamides were first introduced, but the incidence of resistant strains has now become so high that for therapeutic purposes they must be considered insensitive. Meningococci are for the most part highly sensitive, though a few *strains are found to be partially resistant.*

H. influenzæ, *H. pertussis*, the clostridia, pasteurellæ, brucellæ and actinomyces are moderately susceptible. Against organisms of these genera sulphonamides are not therapeutic when given alone and should only be employed in conjunction with a more powerful antibiotic. Sulphonamides are without effect against *Proteus vulgaris*, *Pseudomonas pyocyanea*, viruses and protozoa.

In the presence of localised pus or an overwhelming number of organisms such as may occur in fulminating infections, the minimal concentration that will be effective is considerably raised and dosage must be proportionately higher. In this respect the action of most of the antibiotics, notably penicillin and polymyxin, is superior, and consequently they are usually more effective in *treatment when the number of organisms is large.*

Synergism between penicillin and sulphonamides has been demonstrated in the treatment of certain infections[1] and may also be present when two or more different sulphonamides are employed together.

Para-aminobenzoic acid in minute quantities antagonises the [illegible]

procaine.

Absorption.—Compounds differ in regard to their rate and completeness of absorption from the small intestine. Sulphanilamide, sulphamerazine and sulphathiazole are absorbed rapidly, giving maximal blood levels in three or four hours, while sulphadiazine is absorbed rather less rapidly. Sulphaguanidine is partially (30-60 per cent.) and slowly absorbed. Significant quantities, which may even be sufficient to cause toxic reactions, reach the blood stream. The proportion of phthalylsulphathiazole and succinylsulphathiazole absorbed is only 5 per cent. of the ingested dose, the unabsorbed portion being excreted unchanged in the stools.

Following the application of sulphanilamide powder to granulating surfaces or the peritoneum absorption is rapid and high blood levels may be temporarily reached.

Diffusion.—Sulphonamides diffuse freely into the tissue fluids, serous cavities, fœtal circulation and the cerebro-spinal fluid. In

the cerebro-spinal fluid the concentration ranges from one-half to four-fifths of that in the blood A small amount is excreted in the milk, but with normal doses is insufficient to affect the infant adversely or therapeutically

Excretion.—Excretion in the free and acetylated forms and concentration (20-30 times) take place in the kidneys The rates of excretion of the different compounds differ; a dose of sulphadiazine, sulphanilamide or sulphathiazole is almost completely excreted within twenty-four hours, the rate being most rapid at the third to fourth hour. Less rapid is the excretion of sulphadimidine and slowest that of sulphamerazine The rate of excretion and to some extent the rate of absorption determine the interval to be allowed between doses. If the interval is too long the blood level will at times be sub-optimal. If the interval is too short, especially if the rate of excretion is slow (*e.g.*, sulphamerazine), accumulation takes place in the blood and dangerous levels may be reached. It is recommended that sulphadiazine, sulphanilamide and sulphathiazole should be given four-hourly, sulphadimidine four- or six-hourly and sulphamerazine eight- or twelve-hourly

Solubility of sulphonamide compounds and their acetyl derivatives is many times higher in an alkaline than in an acid urine Sulphacetamide is the most soluble (2,200 mg per 100 c.c at 37°C.), followed by sulphanilamide, sulphadimidine and sulphathiazole.

Sulphadiazine and sulphamerazine are the least soluble, especially in an acid urine, and are, therefore, the most liable to crystallise. (Details of solubility are given in the accompanying table.)

SOLUBILITY IN URINE

(Approximate figures only)

(*Adapted from Medical Research Council War Memo No* 10, 1945)

	Acid Urine (*mg per c c*)	*Alkaline Urine* (*mg per c c*)
Sulphathiazole	100	850
Acetyl-sulphathiazole	10	260
Sulphadimidine	130	330
Acetyl-sulphadimidine	80	210
Sulphamerazine	40	200
Acetyl-sulphamerazine	80	220
Sulphadiazine	17	190
Acetyl-sulphadiazine	50	230
Sulphaguanidine	50	—

safe to continue treatment so long as the volume of urine is adequate and its reaction alkaline.

4. Blood Dyscrasias

The occurrence of agranulocytosis depends more upon the duration of treatment than upon high dosage, onset before the third week being unusual. Leucopenia appears earlier, at any time after the fourth day, and should be suspected if the patient's initial response to therapy is not maintained or if fever recurs during treatment. A total and differential leucocyte count should immediately be performed. Whenever treatment is continued for more than a week the leucocyte count should be repeated twice weekly as a routine. Acute hæmolytic anæmia, which is rarely ... may appear at any stage

[illegible]

excretion encouraged by the administration of alkalies and fluids as already described. For hæmolytic anæmia, vitamin B complex should be injected or given by mouth as brewer's yeast (1 drachm mixed with boiling milk and allowed to cool, three times daily).

Leucopenia due to the disease is in itself no contraindication to *sulphonamide therapy.*

5. Neuritis

... and has been attributed ... *tra-*

[illegible]

6. Miscellaneous Intoxications

Among the other reactions reported are hepatitis and pleural effusion [2]

Acquired Resistance

Sulphonamide-resistant strains emerge under conditions of incomplete bacteriostasis. In practice inadequate dosage and the presence of large numbers of organisms or undrained pus are the most frequent causes. Acquired resistance is found among gonococci, pneumococci, meningococci, *Bact. coli*, streptococci and dysentery bacilli. In severe infections and in those which do not respond favourably, or relapse under treatment without obvious

[illegible] in determining [illegible]

of treatment must be optimal. The principle of employing a high initial dose and a maintenance dosage in proportion to the severity of the infection and the sensitivity of the organism must be observed. When indicated, such measures as surgical drainage, diuresis or combined therapy should be utilised to the best advantage. They are often essential for securing complete eradication of the organism.

Administration

Sulphonamides are given by mouth for their systemic effect and for their effect against intestinal pathogens. The soluble sodium salts of sulphadimidine, sulphadiazine, sulphathiazole and sulphamerazine may be injected by the intravenous or deep intramuscular routes when rapidity of action is essential and when oral administration is impracticable by reason of vomiting or impaired consciousness. Application to wounds and the peritoneum at operation may be employed, but to the skin should be avoided. Intrathecal injection is contraindicated.

Dosage

[illegible]

least risk from toxicity.

In general, infants require and tolerate a higher dosage, weight for weight, than adults.

Modifications of the recommended scale of dosage are necessary in the treatment of urinary tract infections, and these are described [illegible]

Summary

The preferred sulphonamide is that which is most active against the infecting organism (see notes on page 13), and in all severe infections the choice should be supported by determination of the sensitivity of the organism. If individual conditions (oliguria,

sensitisation, etc.) exaggerate a tendency to toxic reactions from a particular compound, it is advisable to employ a compound which will minimise the risk. Dosage must be sufficient to obtain the maximal therapeutic effect, and administration arranged to fit in with any proposed ancillary treatment. The measures to be taken for prevention of reactions, summarised below, have already been described in greater detail.

1. [illegible]
2. [illegible]
3. [illegible]
4. Employment of a soluble compound or combination of compounds.
5. Rational therapeutic régime.
6. Limitation of treatment to seven days (except in exceptional circumstances).
7. Total and differential leucocyte count twice weekly if course exceeds seven days.
8. Total and differential leucocyte count if fever returns [illegible]
9. [illegible]
10. Ensuring an adequate intake of vitamin B complex.
11. Avoiding further sulphonamide therapy if serious intoxications have occurred.

Sulphones

The sulphone compounds are allied chemically to the sulphonamides and have in common certain pharmacological properties. [illegible]

promizole, sulphetrone and others have been prepared. DADPS, promizole and sulphetrone are most widely employed, as they cause fewer and usually less severe reactions.

Pharmacology

The sulphones inhibit growth of *Mycobacterium tuberculosis* and *Streptococcus pyogenes*, while in addition DADPS is active against *Streptococcus pneumoniæ*. The degree of efficiency against streptococci is comparable to that of sulphanilamide. Against *Myc.*

TABLE OF SULPHONAMIDE DOSAGE

Compound		Loading Dose					First 48 Hours					Maintenance					Therapeutic Blood Concentration
	Age (years)	12+	5–12	2–5	1–2	0–1	12+	5–12	2–5	1–2	0–1	12+	5–12	2–5	1–2	0–1	
Sulphadiazine Severe	Oral or Injected	2–4	1	0·75	0·5	0·5	1·5 (4)	1 (4)	0·75 (4)	0·5 (4)	0·5 (6)	1 (4)	0·5 (6)	0·5 (6)	0·25 (6)	0·25 (8)	
Mild	Oral	2 2	1 1	0·75 0·75	0·5 0·5	0·5 0·5	1 (4)	0·75 (4)	0·5 (4)	0·5 (6)	0·25 (6)	1 (8)	0·5 (6)	0·25 (6)	0·25 (8)	0·25 (8)	10–15 mg per ml.
Sulphamerazine Severe	Oral	3–4	2	1·5	1	0·75	1·5 (8)	1·5 (12)	1 (12)	0·75 (12)	0·5 (12)	1 (8)	1 (12)	0·75 (12)	0·5 (12)	0·25 (12)	
Mild	Oral	3	1·5	1	0·75	0·5						1 (8)	1 (12)	0·75 (12)	0·5 (12)	0·25 (12)	10–15 mg. per ml.
Sulphadimidine (Sulphamezathine) Sulphatriad Severe	Oral or Injected	3–6	2·5	2	1·5	1	2 (4)	1·5 (6)	1·25 (6)	0·75 (6)	0·5 (6)	1·5 (4)	1·25 (6)	1 (6)	0·75 (6)	0·5 (6)	
Mild	Oral	3 3–4	2·5 2·5	2 2	1·5 1·5	1 1						1·5 (4)	1·25 (6)	1 (6)	0·75 (6)	0·5 (6)	10–15 mg. per ml.
Sulphathiazole Sulphacetamide Severe	Oral or Injected	2–4	1	0·75	0·5	0·5	1·5 (4)	1 (4)	0·75 (4)	0·5 (4)	0·5 (6)	1 (4)	0·5 (4)	0·5 (6)	0·25 (4)	0·25 (6)	
Mild	Oral	2 2	1 1	0·75 0·75	0·5 0·5	0·5 0·5	1 (4)	0·75 (4)	0·5 (4)	0·5 (6)	0·25 (4)	0·75 (4)	0·5 (4)	0·25 (4)	0·25 (6)	0·25 (6)	4–7 mg. per ml
Sulphaguanidine Sulphasuccidine													1·5	1	0·75	0·5	(5–10 mg. per ml. on the quoted dosage)

The figures in parentheses denote the interval in hours between doses. Doses are given in grammes.
(For duration of treatment refer to specific disease and page 18.)

tuberculosis it is inferior to that of streptomycin both experimentally and in the treatment of the human disease. In the treatment of leprosy, on the other hand, sulphones are greatly superior to streptomycin. The effective concentration in the blood differs for each compound—DADPS 1 mg. per 100 ml., diasone and promin 2 mg. per 100 ml., sulphetrone 5 mg. per 100 ml., promizole 1-2 mg. per 100 ml. The order of therapeutic efficiency is thought to be (1) DADPS, sulphetrone and promizole, (2) promin and diasone.

Synergism between streptomycin and sulphetrone[3] has been demonstrated in experimental tuberculosis and may also occur in the human disease, between promizole and streptomycin.[4]

Absorption.—Following oral ingestion, therapeutic concentrations are present in the blood from the sixth to the twelfth hour with sulphetrone and to the twenty-fourth hour with DADPS. The dose required to achieve a therapeutic level varies according to the drug used and from patient to patient. The concentration in the blood is increased by constipation, which establishes a reservoir of the drug in the lower intestine, thus increasing reabsorption, and by reduced urinary output, which diminishes excretion.

Diffusion.—The sulphones diffuse rapidly and completely into all vascular tissues except the brain. Appreciable concentrations reach the cerebro-spinal fluid after injection and oral administration.

[illegible] mainly in the urine an [illegible] ough the lo[illegible] d by the *kidneys is proportionate to the volume of urine and is present in a* concentration many times higher than that in blood.

Toxicity.—The toxic reactions associated with sulphone *therapy, while numerous, are for the most part preventable by* adherence to a suitable routine of management. In addition to [illegible] indirect reactions [illegible] orp- [illegible] —are encountered.

General Effects

trone. In practice, safe concentrations should be maintained by a constant dosage, by restricting the fluid intake to 3 pints daily, by ensuring a normal bowel action each day and by estimating the blood level weekly. Symptoms of acute toxicity require immediate investigation and treatment. The blood level must be estimated [illegible]

continued until the concentration in the blood has been reduced and toxic manifestations have disappeared or been corrected

Cyanosis

Patients taking sulphones by mouth acquire a characteristic [illegible]

tration rises above 1 mg per ml.,[6] hæmolysis is often of a severity to necessitate discontinuing treatment

Hypersensitivity Reactions

Skin rashes and allergic rhinitis are encountered, which are usually of little importance Occasionally, however, dermatitis may progress to exfoliation [5]

Goitrogenic Effect

Of the sulphones, promizole is the only compound liable to cause enlargement of the thyroid gland The disturbance of physiology is thought to be the same as that utilised in the treatment of thyrotoxicosis with thiouracil and allied preparations.

Iron Deficiency Anæmia

As sulphones, when given by mouth, form an insoluble compound with iron in the intestine, the amount of iron absorbed is reduced, with the result that hypochromic anæmia may develop. A suitable iron preparation (e g , ferrous sulphate gr. 9 each day in divided doses) should therefore be administered prophylactically as a routine. An established hypochromic anæmia, with the hæmoglobin level below 60 per cent. of normal, is an indication for discontinuing oral sulphone therapy.

Vitamin B Deficiency[3]

The sulphones, especially DADPS, promin and diasone, may cause peripheral neuritis, hæmolytic anæmia and liver damage. It is believed that deficiency of vitamin B complex, brought about by interference with intestinal biosynthesis, is responsible, since [illegible]

[illegible] incidence of these reactions is much reduced by correcting nutritional and possible vitamin deficiencies before sulphone therapy is commenced.

Disturbance of the Alkali Reserve

The sulphones tend to cause alkalosis, which is, however, fully compensated in patients who have been under treatment for long periods. Disturbance can be avoided by gradation of dosage during the first two to five weeks of treatment. For instance, [illegible]

[illegible] three times daily.

Lepra Reactions

Lepra reactions, including iridocyclitis, are seen most commonly in patients in poor general health and particularly at the start of treatment.[7] *Preliminary attention to nutrition materially reduces* their incidence During administration of DADPS a syndrome comprising lepra reactions, psychosis, neuritis and headache, sometimes associated with exfoliative dermatitis, has been reported.[8]

Administration

Sulphetrone may be given orally or by intramuscular injection when it is *necessary to continue treatment in the presence* of iron or vitamin deficiencies Promin, being excessively toxic when given orally, should be given intravenously[9] and diasone may be given by either route. Sulphetrone may be injected with safety intrathecally, alone or in conjunction with streptomycin.

Dosage

Oral administration should be commenced at low dosage increasing over a period of two to five weeks, until, as a state of

olerance becomes established, full dosage is reached An induc-
ion period of five weeks is recommended for DADPS[8] and two
o three weeks with sulphetrone[10]

TABLE OF DOSAGE

	Dose	Therapeutic Blood Level per 100 ml
Promin	up to 5 gm. daily intravenous	2 mg
Diasone	up to 2 gm daily oral or i v	2 mg
Promizole	up to 6 gm daily oral	1 2 mg
Sulphetrone	up to 9 gm daily oral or i m	5 12 mg
DADPS	100 mg daily oral	1 mg

It is now thought that equally good results may be obtained with less risk of toxicity in leprosy by employing smaller doses Details are given below.

The duration of treatment of leprosy varies with the stage of the disease when treatment is instituted and with the time taken to produce negative bacterioscopic results This will be as a rule from six months to two years [7] The duration of courses of promin diasone therapy must be short, on account of the frequency l severity of toxic reactions

ORAL DOSAGE IN LEPROSY[11]

	First Week	Second Week	Third Week	Fourth Week	Fifth Week
Sulphetrone (daily)	1 gm	2 gm	3 gm	3 gm	3 gm
Diasone (daily)	0 3 gm.	0·6 gm	0·9 gm	0·9 gm	0·9 gm.
DADPS (daily, for 6 days each week)	50 mg	50 mg	100 mg	100 mg	100 mg.
DADPS (bi-weekly)	100 mg	100 mg	200 mg	200 mg	300 mg

SUMMARY

DADPS and sulphetrone and promizole are preferred, as they may be administered over long periods with little risk of severe toxic reactions, provided that the following precautions are taken.

Chapter III

PENICILLIN

Four penicillins, F, G, K and X, derived from moulds of the genus *Penicillium*, are known. Penicillin G is superior in therapeutic activity to penicillins F and K and is that in general use. Penicillin X, though more potent than penicillin G, is not produced on a commercial scale.

Penicillin is prepared in amorphous form or as the crystalline calcium, sodium or potassium salts; the latter, being purer and more stable are preferred in medicine.

Storage

Full potency of crystalline penicillin in the dry state is retained for about three years at room temperatures and for longer at 0° to 4°F. The potency of penicillin solution diminishes after forty-eight hours at room temperatures and after one week with refrigeration. The potency of amorphous penicillin is lost more rapidly than that of the crystalline salts.

Pharmacology

[illegible]

are sensitive to low concentrations—*i.e.*, less than 1 unit per ml.:

[illegible]

Cl. tetani, Cl. welchii, Cl. septicum, Cl. botulinum), spirochætes (*Trep. pallida, Trep. recurrentis, Trep. pertenue, Trep. vincenti*), leptospiræ (*Lepto icterohæmorrhagiæ* and *Lepto. canicola*), *Spirillum minus, Bacillus subtilis* and *Bacillus anthracis*. *Actinomyces bovis, Hæmophilus influenzæ* and *Erysipelothrix rhusiopathiæ* are variably sensitive to concentrations above 2 units per ml. Occasional strains of enterococci and *Proteus vulgaris* are found to be inhibited by 10-20 units per ml. *Streptococcus fæcalis* is usually insensitive to less than 40 units per ml. and is thus unaffected in the body,

except by the high concentrations that may be reached in the urine.[1] Against this organism aureomycin is much superior to

[illegible]

The mode of action of penicillin is, under favourable circumstances, bactericidal in contrast to the usual modes of action of aureomycin, terramycin and chloramphenicol which are suppressive. On this account it is often more effective in practice, as for example in the treatment of subacute bacterial endocarditis.[3] Synergism is reported to be present with streptomycin against *Str faecalis*[3] and with aureomycin against *Staph aureus* [3] Thus in the treatment of bacterial endocarditis due to *Str faecalis*, penicillin with streptomycin appears to be very effective, and is probably superior to aureomycin [2]

It is of the utmost importance to have the penicillin-sensitivity estimated if the disease is severe and the organism of a type (*e g.*, staphylococci or viridans streptococci) in which variations in sensitivity are known to occur The concentration in contact with the organism must, for successful treatment, exceed that shown to be necessary *in vitro* It was previously held that this concentration must be continuously maintained, but there is some evidence to support the view that high intermittent concentrations may be just as satisfactory [4]

Absorption.—Aqueous solutions of penicillin are absorbed slowly and inconstantly from the upper intestine The dosage required to give blood levels comparable to those obtained after injection is at least five times the intramuscular dose. Destruction [illegible]

hour After injection of 50,000, 100,000 and 500,000 units, blood levels reach a maximum of 2, 3 and 4 units per ml, which fall to 0·03, 0·06 and 2 units respectively at the fourth hour At the twelfth hour, after doses of 50,000 and 100,000 units, none is detectable in the blood, but after 500,000 units about 0 25 unit remains. Thus by the use of larger doses therapeutic concentrations may be maintained for longer periods Depot preparations, in smaller dosage, have the advantage that adequate levels are maintained for about twenty-four hours, though they are reached only after several hours. It follows that when a depot penicillin is given for the treatment of an acute infection, the initial dose should always be

combined with a full dose of crystalline penicillin to ensure a rapid effect.

Diffusion.—Penicillin diffuses readily into the pleural, peritoneal and joint cavities. The local concentration, however, is always somewhat lower than that in the blood, and should be augmented by injection into the infected cavity whenever practicable. Diffusion into the cerebro-spinal fluid is poor unless the permeability of the meninges is increased by inflammation. After massive intramuscular doses (*e.g.*, 2 to 4 million units), but *not after average doses, effective levels are obtained.*

The concentration of penicillin in the tissues lags behind that in the blood and does not show the same steep fluctuations during intermittent therapy. Less frequent injection (*i.e.*, twelve-hourly), therefore, maintains adequate local concentrations.

The antibiotic passes readily into purulent exudates without loss of potency, and in this respect differs from the sulphonamides and streptomycin. It traverses the placenta freely and reaches the fœtal circulation in therapeutic quantities. Diffusion into the less vascular structures, such as bone, brain and cartilage, is slow and incomplete. Penicillin diffuses poorly into the sputum. On the other hand, "Estopen" (penicillin G hydriodide ester) reaches therapeutic concentrations in the sputum and gives high levels in the lung. It thus appears to possess advantages in the treatment of pulmonary infections.[5]

Excretion.—Sixty per cent. of circulating penicillin is excreted in an active form by the kidneys and is at the same time greatly *concentrated. A daily dosage of 100,000 units,* if the volume of urine does not exceed 1·5 litres, may be expected to give urinary levels of 40 units per ml.

Renal insufficiency delays excretion, causing high and prolonged blood levels and low concentrations in the urine. The same effect may be obtained by the administration of caronamide by mouth. [illegible] high

te

ie

fæces.

SIDE EFFECTS

Pure penicillin is a non-toxic substance; the toxic dose of calcium penicillin is certainly in excess of 10,000,000 units. Reactions seen during its administration are due to impurities or to sensitisation by previous contact with penicillin or other fungi.

Hypersensitivity Reactions

Urticarial and morbilliform rashes, sometimes associated with fever and occasionally with pain and effusion into joints, occur usually in patients who have received a high dosage of systemic penicillin over a long period or who have previously been in contact with the drug. It is probable that fortuitous contact with other fungi may also cause sensitisation. Patients who exhibit other manifestations of allergy seem rather more prone to reactions from penicillin than do normal persons.[4] Symptoms cease rapidly on withdrawing the drug and are relieved by antihistamine drugs The impurities in earlier penicillin preparations and the oily bases used in depot preparations may themselves produce symptoms

Local Reactions

Local pain frequently accompanied injection of the earlier and comparatively impure products, but since crystalline penicillin has become widely available, such reactions are rarely seen They are now more often due to the introduction of penicillin-insensitive organisms, such as *Bact. coli*, *Staph. aureus*, or even, very rarely, the tubercle bacillus Depot penicillins in oily bases are, however, liable to cause some local reaction. Stomatitis is frequently seen in patients taking penicillin lozenges if the prescribed amount is exceeded.

Herxheimer-like Reactions

In both congenital and acquired syphilis acute exacerbation in the severity of the disease may occur when treatment is commenced at full dosage. By employing for the first three days of treatment small but increasing doses, or by preliminary iodide and bismuth therapy, the risk is probably reduced (For further details see Chapter 17, page 131.)

Effect on the Pregnant Uterus

It has been stated that bleeding and uterine contraction may follow the administration of penicillin during pregnancy. The cause has not been fully established, but may well be due to impurities rather than to penicillin itself.

The risk to pregnant women appears to be very slight and should not influence the decision to employ penicillin.[7]

Meningeal Irritation

Intrathecal injection of single doses higher than 25,000 units may cause a mild aseptic meningitis, which increases in frequency and severity as the dosage is increased. Discontinuing therapy by this route is followed by disappearance of abnormal signs.

Resistance

Acquired resistance to penicillin is less frequent and of a lower order than that encountered with streptomycin. The minimal concentration necessary for inhibition is commonly increased only two or four times. Thus, therapeutic concentrations may still be [illegible] however, the [illegible]

centrations reached in the body are ineffective. As the incidence of staphylococcal infections which are now penicillin-resistant is between 5 and 10 per cent., the chance of encountering an initially insensitive strain is considerable. It is therefore important to estimate the sensitivity at the start of treatment rather than risk failure, especially when, as in severe infections, delay would be dangerous. Under these circumstances it is advisable to start treatment with both penicillin and aureomycin. Depending on the *in vitro* sensitivity, the physician may then either continue with penicillin alone, if necessary increasing the dose, or continue with aureomycin, chloramphenicol or streptomycin. If the degree of insensitivity to all is high, it may be necessary to give both penicillin and aureomycin, taking advantage of their synergistic action.[8]

Increases in resistance during treatment with penicillin are not of sufficient magnitude to cause relapses or failure of treatment, so long as initially adequate concentrations are maintained.

Administration

Penicillin being a pure, soluble, non-irritant substance, may be administered by any recognised route. The preferred route of [illegible] intramuscular, which is [illegible]

prophylaxis and for the treatment of mild infections by sensitive organisms. By this route the antibiotic is best given in a buffered

aqueous preparation twenty minutes before feeds. The intravenous route, though safe, is seldom necessary, since the effect of intramuscular injection of crystalline penicillin is sufficiently rapid even for hyperacute infections.

In the treatment of meningitis crystalline penicillin is injected intrathecally, cisternally, or into the lateral ventricles of the brain. Injection into infected joints or the pleural cavity is employed as an adjunct to systemic therapy to secure adequate local concentrations. Injection into abscess cavities, after withdrawal of the pus to avoid unnecessary dilution, is also of value.

Inhalation of penicillin in solution by means of a suitable inhaler is widely used to control bronchial infection and reduce the volume of sputum in bronchiectasis.

Penicillin may be applied to wound surfaces, mucous membranes or eyes in suitable bases, and to the skin for short periods.

Depot penicillins should be injected intramuscularly and never intravenously, subcutaneously, or into the subarachnoid spaces.

DOSAGE

For the treatment of acute systemic infections, the initial dose should contain crystalline penicillin, in order to obtain therapeutic blood levels without delay. The first dose may, if so desired, be combined with the first injection of a depot penicillin, such as "Distaquaine G fortified." In fulminating systemic infections an initial loading dose of twice the amount to be given at each subsequent injection is recommended.

In the accompanying table are given suitable doses of penicillin for the treatment of severe and moderately severe infections by penicillin-sensitive organisms. Infections by partially sensitive organisms, whether suspected or proven, require higher doses, according to their degree of sensitivity. Higher dosage is also required if the infected tissue is one through which penicillin diffuses poorly—*e.g.*, the meninges. The relatively small variations in concentration that occur in the tissues permit the interval between doses of crystalline penicillin to be lengthened to twelve hours in the treatment of localised infections. For systemic infections the interval will normally be three, four or six hours, but with higher doses, as recommended in the accompanying table, longer intervals may be allowed.

The duration of treatment depends on the nature of the disease and is further considered in the appropriate sections. In acute infections of moderate severity, therapy may be discontinued when the temperature has remained normal for forty-eight hours.

Chapter IV

STREPTOMYCIN AND NEOMYCIN

Streptomycin

STREPTOMYCIN is an antibiotic derived from the soil fungus, *Streptomyces griseus*. For clinical use it is prepared as the crystalline sulphate, hydrochloride or calcium chloride complex. Dihydrostreptomycin—a derivative of streptomycin—is similar in antibacterial activity, but was reported to cause less damage to the eighth nerve.[1]

STORAGE

At room temperatures, dry streptomycin and dihydrostreptomycin in unopened containers retain their potency for two years, whereas prepared solutions lose their potency after a week. Furthermore, as bacterial contamination may occur during preparation, solutions should not be made up until required.

PHARMACOLOGY

[illegible] activity parti-

[illegible]

negative organisms sensitive to streptomycin in low concentrations (0·5 μg. per ml.) are *Bacterium coli*, *Hæmophilus influenzæ*, *Hæmophilus pertussis*, *Hæmophilus ducreyi*, the shigellæ (*Sh. shigæ*, *Sh. flexneri*, *Sh. sonnei*), *Bacterium friedländeri*, leptospiræ, the brucellæ (*Br. tularense*, *Br. melitensis*, *Br. abortus*), meningococci, gonococci, *Proteus vulgaris* and salmonellæ. The mode of action against *H. influenzæ*, *Bact. coli* and *H. pertussis* with concentrations greater than 10 μg. per ml. is bactericidal,[2] and probably against *Myc. tuberculosis* in the concentrations obtained by standard dosage.[3] In lower concentrations its action is bacteriostatic. Dihydrostreptomycin is thought to be less active than streptomycin, but in therapy the difference, if it exists, is small.

Certain Gram-positive organisms—namely *Str. pyogenes*, viridans streptococci, staphylococci, pneumococci, *C. diphtheriæ*, *B.*

anthracis, *Actinomyces bovis* and spirochætes—are moderate sensitive. *Ps. pyocyanea* is but slightly affected.

The clostridia, viruses, rickettsiæ, fungi and protozoa ar insensitive to streptomycin. It is of interest that, in contrast to the sulphones, the antibiotic is ineffective in the treatment of leprosy. *Myc. tuberculosis* is sensitive to concentrations between 1 and 6 µg. per ml. Highly resistant strains of many micro-organisms, including *Myc. tuberculosis*, may emerge during treatment and are a potent cause of therapeutic failure. Furthermore, the surviving organisms may be the source of resistant infection in others.

Synergism has been demonstrated between streptomycin and other antibiotics—*e.g.*, against *Myc. tuberculosis* with sulphetrone[4] and promizole[5] and against *Str. fæcalis* with penicillin.[6]

Absorption.—To obtain therapeutic concentrations in the blood, streptomycin and dihydrostreptomycin are injected intramuscularly, as absorption from the intestine does not take place. After intramuscular injection of 1 gm. the concentration in the blood is maximal (20 to 40 µg. per ml.) between one and two hours. Two grams given in the twenty-four hours intravenously maintains serum levels of about 30 µg. per ml.[7] The rate at which the concentration diminishes is relatively slow, small amounts are detectable in the serum after about twenty-four hours.

Diffusion.—Streptomycin diffuses rapidly into serous cavities, e vascular tissues of the body, and across the placenta into the tal circulation. Little traverses the meninges unless their permeability is increased by inflammation. Only then may intramuscular administration give therapeutic concentrations in the cerebro-spinal fluid.

Excretion.—Excretion of the antibiotic in an active form by the kidneys accounts for 50 to 75 per cent. of an injected dose. Less than 5 per cent. is excreted in the bile and the fate of the remainder is unknown.[7] On a daily intramuscular dose of 2 gm. the concentration in the urine varies according to the volume of urine between 0.5 and 2 mg. per ml. On a daily oral dose of 2 gm., the concentration in the fæces varies between 0·5 and 1 mg. per ml.[7] Thus the concentrations reached in both urine and fæces are sufficient for all except highly resistant organisms. As with other antibiotics excreted by the kidney, renal failure delays excretion, causing prolonged high blood levels and low urinary concentrations.

TOXICITY

Streptomycin and dihydrostreptomycin possess a specific

means the emergence of resistant strains is much delayed (prevented.

Without knowledge of the streptomycin-sensitivity the thera peutic blood concentration and the requisite dosage can only b [illegible]

In estimating dosage, it should be remembered that the efficacy (streptomycin is reduced in the presence of pus and large bacteri populations. For this reason, reduction of the number of organism by surgery or other appropriate means is an important and ofte indispensable part of treatment.

ADMINISTRATION

For the treatment of systemic infections, streptomycin i injected by the intramuscular route. Oral administration i employed only for eradication of organisms within the intestine Intrathecal injection by the lumbar, cisternal or intraventricula route is necessary in the treatment of meningitis. Local applicatio to infected wounds and tuberculous ulcers has been tried, but it value without systemic therapy is uncertain Streptomycin ma be injected into the pleural cavity for the treatment of tuberculou empyemata, and into caseous glands at the time of incision.

DOSAGE

The schedule of dosage for the treatment of acute infection differs from that employed in tuberculosis. In the former the course of treatment should be intensive and short (usually no longer than ten days). Dosage may be calculated on the basis o 20 mg. (20,000 units) per pound daily.[8, 10, 11] If a therapeutic [illegible]

The intrathecal dose must be sufficient to maintain levels in the cerebro-spinal fluid which exceed those found to be inhibitory *in vitro*. One hundred mg. for adults and 50 mg. for children, given twice daily, will produce levels above 25 units per ml.[11]

In tuberculosis the standard daily dose for an adult is 1 gm given in one injection. Doses up to 2 gm daily may under certain circumstances be justifiable for short periods. By spacing doses at longer intervals, even on alternate days or every third day, therapeutic efficiency is not affected, but the onset of deafness and the emergence of resistant strains are delayed. To minimise the risk of relapse through the emergence of resistant strains it was previously held that treatment should normally be limited to about six weeks, but it has been found that by the employment of combined therapy (para-aminosalicylic acid or sulphones), and wider spacing of injections, courses of at least six months' duration may be given with little risk.

The intrathecal dose for adults is 100 to 150 mg, for children 50 mg, and for infants 25 mg in 2 to 4 ml of water.

STREPTOMYCIN DOSAGE

Age	For Acute Non-tuberculous Infections		For Tuberculosis
	12 hourly	*6 hourly*	*Daily or alt. day*
0–1	200 mg	100 mg	200 mg
1–2	300 mg	150 mg	200 mg
2–5	400 mg.	200 mg	250 mg
5–12	500 mg	250 mg	500 mg
12 and over	1–1.5 gm	500–750 mg	1 gm

For duration of treatment refer to section on specific infection.

Neomycin

Neomycin is an antibiotic derived from a soil fungus, *Streptomyces fradiæ*, and is thought to be similar in potency and range of antibacterial activity to streptomycin.

PHARMACOLOGY

Neomycin is a soluble heat-stable substance, active against numerous Gram-negative, some Gram-positive organisms and *Myc. tuberculosis*. Against Gram-positive and negative organisms the activity is similar to that of streptomycin.[11] Against *Proteus* and *Bact. aerogenes*, however, it appears to be superior.[12] In general, it appears to be less effective experimentally than streptomycin against *Myc. tuberculosis*, with the exception of a few strains which are more sensitive to neomycin.[13]

It is equally active against streptomycin-sensitive and insensitive strains[13] and cross-resistance is not acquired.[15] Its mode of action is bacteriostatic in low concentration and bactericidal in slightly higher concentration. This margin appears to be less than that of streptomycin.

Toxicity

Neomycin is not free from toxicity, though present difficulties in obtaining the pure substance prevent accurate assessment. The sudden onset of deafness in four out of six patients after four to six weeks' treatment and transient nephrotoxicity are reported, but it was considered that impurities rather than neomycin may have been responsible.[16]

Resistance

Acquired resistance to neomycin is of the "penicillin type" in which relatively small increases occur. The "streptomycin type" of acquired resistance has not been found.

Bibliography

Streptomycin

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Chapter V

POLYMYXIN

FROM various strains of *Bacillus polymyxa* have been isolated the antibiotics polymyxin A (aerosporin), B, D and E. They possess the same antibacterial range, but differ in regard to potency and toxicity. Polymyxin E is virtually free from serious side effects and is therefore preferred to polymyxins A, B or D.

PHARMACOLOGY

The polymyxins are active against certain Gram-negative organisms and in general are more effective than other antibiotics,[1] particularly against *Pseudomonas pyocyanea*. Among those sensitive to concentrations below 2 µg. per ml. are *Bacterium coli*, *Ps. pyocyanea*, *Bacterium friedländeri*, *Hæmophilus influenzæ*, *Hæmophilus pertussis*, *Bact. aerogenes*, the dysentery group and *Vibrio choleræ*. The salmonellæ and brucellæ are sensitive *in vitro*, though, for practical purposes, unaffected in animals.[2] Meningococci and gonococci are partially sensitive, but are more sensitive to other available agents. *Proteus vulgaris*, the Gram-positive cocci, rickettsiæ and viruses are insensitive.

Pure polymyxins A, B and E are believed to be similar in potency but superior to polymyxin D.[3]

Absorption.—Absorption from the intestinal tract is so poor that it may be considered not to take place.

Intramuscular injection of 0·5 mg. per kilogram of body gives therapeutic blood levels (*i.e.*, above 1 µg. per ml.), and 1 mg. per kilogram gives levels up to about 10 µg. per ml. from the first to fourth hour in children.[4] Somewhat higher levels may be reached after repeated injections. Assayable concentrations appear in the blood after application of the antibiotic to granulating surfaces.

Diffusion.—Polymyxin diffuses readily into vascular tissues, but does not pass into the cerebro-spinal fluid. Its distribution in the tissues has not been fully studied.

Excretion.—Polymyxin is excreted principally by the kid and only a small proportion by other routes.

TOXICITY.—Specific reactions, which are believed to be due to inherent toxicity, are encountered with certain strains of polymyxin. Polymyxin E in therapeutic dosage is practically free from side effects and is thus preferred to polymyxin A, B or D.

LOCAL REACTIONS

Local redness, swelling and pain, usually accompanied by low or moderate pyrexia, frequently appear at the site of intramuscular injection of polymyxin B, but rarely of A or E. As this is less evident with the more recent preparations, it is possible that impurities rather than polymyxin itself may be the cause. These reactions are a source of discomfort to the patient and may be sufficiently severe to warrant discontinuing therapy.

NEPHROTOXICITY

Polymyxins A and D cause, in most patients, albuminuria, microscopical hæmaturia and cylinduria, which disappear when the antibiotic is withheld. A minor degree of nitrogen retention may also be found Although these manifestations are temporary they are, nevertheless, a drawback to the use of these particular agents for the treatment of mild or self-limiting infections.

REACTIONS

NEUROLOGICAL.—Transient paræsthesiæ, hypæsthesiæ, mild dizziness and weakness have been reported with polymyxin B and E.[5] They appear to be of little importance and do not warrant stopping treatment.

MENINGEAL REACTIONS.—Intrathecal injection of polymyxin E, in doses higher than those recommended, causes non-specific meningeal irritation which is similar in character and severity to that encountered with penicillin or streptomycin.[6]

RESISTANCE

Acquired resistance has not been demonstrated following the administration of polymyxin This finding is in accordance with its bactericidal mode of action, and with the laboratory evidence that resistant strains do not grow out in the presence of suboptimal concentrations.

ADMINISTRATION

Polymyxin is injected by the intramuscular route to achieve a systemic effect. Oral administration is employed only for eradica-

tion of sensitive organisms within the intestine. Infected burns and granulating surfaces may be treated with local applications of 1 per cent. polymyxin cream or 0.1 per cent. aqueous polymyxin spray.[7] For the treatment of meningitis, the antibiotic is injected by the lumbar or intraventricular routes.[6]

Dosage

The intramuscular dose of polymyxin E for adults lies between 25 mg. and 50 mg. The higher dose is necessary when the infection is severe or if the patient is above average weight. The dose for children may be calculated on the basis of 0.5 to 1 mg. per pound of body weight (four-hourly) according to severity.

In order to maintain therapeutic blood concentrations, four-hourly injections are thought to be necessary, and this interval has been adopted in practice. Individual oral doses may be calculated on the basis of 1 to 2 mg. per pound of body weight, every four hours.

Intrathecal injection, once or twice daily, of 4 mg. (40,000 units), in 3 ml. of distilled water for children below the age of 4 years, gives levels above 10 units in the cerebro-spinal fluid. The dose for adults and older children has not been determined.

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tinuing treatment. Pre-existing intestinal disturbances, such as ulcerative colitis, may be aggravated by chloramphenicol, and the antibiotic should not therefore be routinely administered to such patients, unless the rôle of the bacterial flora is considered to be important.

Normal synthesis of vitamin B is thought to be prevented by the action of chloramphenicol in suppressing intestinal coliform organisms. While the manifestations encountered during treatment closely resemble those caused by vitamin B deficiency, the rapidity with which they may appear favours the view that a different mechanism is involved. Prolonged and repeated courses of treatment increase their incidence. Most commonly encountered are stomatitis and glossitis, often originating as a vesicular eruption on the uvula. Vaginitis, vulval and anal irritation may also occur and be most persistent. *Monilia albicans* can usually be isolated from these lesions. Growth of monilia is apparently encouraged by the altered environment, and generalised mycosis has been reported.[6]

Whole yeast or an active substitute should be administered orally to all patients whose courses of treatment exceed five days. Injection of vitamin B complex, however, is thought to be more effective and is recommended for the treatment of established lesions.[7] Locally, 1 per cent. aqueous gentian violet or zinc cream should be applied. Lesions which are refractory may necessitate discontinuing treatment. Substitution of aureomycin for chloramphenicol brings no benefit.

Hypersensitivity Reactions

Urticaria or transient erythema, affecting areas exposed previously to sunlight and associated with tachycardia and chills, may occur,[1] but appear to be uncommon

Herxheimer-like Reactions

The severity of typhoid fever may be temporarily increased on instituting a full dosage régime. Induction with sub-optimal doses during the first twenty-four hours is effective in prevention of this reaction.

Hæmatological Changes

Leucopenia, which disappears on stopping treatment, has been recorded.[8] It seems, however, to be uncommon and is no contra-

indication to further administration of the antibiotic. Vaginal and rectal hæmorrhage have also been encountered.[8]

Cerebral Stimulation

Large doses of chloramphenicol (3 to 4 gm.) may cause a minor degree of cerebral stimulation and even euphoria, rarely confusional states occur at an early stage of treatment.

Effect on the Host's Cells

[illegible] ductory chapter, the possible significance in human therapeutics has not been studied. The "muscle fatigue syndrome," probably caused by interference with muscle cell metabolism, has been reported in man with therapeutic dosage.[11]

Resistance

Experience with other antibiotics, whose mode of action resembles that of chloramphenicol, favours the possibility that resistant micro-organisms may emerge after contact with suboptimal concentrations of the antibiotic. The incidence appears to be low and at the present time is of little importance in therapy. An increase in resistance of about threefold in *Salm. typhi*, isolated in a relapse, has, however, been recorded.[11] As a precaution it is advisable to ensure complete bacteriostasis by giving an effective dosage for a sufficient period and by making full use of other adjuvant measures that may be appropriate in special circumstances.

Administration

Chloramphenicol is given by mouth or, if this is impracticable, rectally. The antibiotic, being intensely bitter, is dispensed in capsules.

Infants under the age of six months do not object to the taste, and will usually take the powder itself mixed with their feeds. Administration of the capsules by mouth to children between the ages of six months and five years often presents great difficulties;

in these circumstances, insertion of perforated capsules into the rectum or administration by œsophageal tube may be employed.

As solubility is low, the antibiotic is unsuitable for injection. The value of local application is at present undetermined.

Dosage

It is recommended that an initial loading dose, followed by maintenance doses every four to six hours, be used for all infections. The optimal duration of therapy depends on the nature of the [illegible]

relapse is passed

The initial loading dose for adults may be calculated on the scale of 10 to 20 mg. per pound of body weight, according to severity For infants the dosage should be 20 to 25 mg. per pound of body weight. It is preferable to give the initial dose, especially if large, in three parts at hourly intervals.

Maintenance dosage should be on the basis of 10 to 15 mg. per pound of body weight for children and 7·5 to 10 mg. for adults, every six hours. In severe and fulminating infections or in those infections where experience has shown that the response is uncertain it is imperative to estimate the bacterial sensitivity. Optimal dosage, which may be higher than that quoted, can then be determined with greater confidence.

CHLORAMPHENICOL

TABLE OF DOSAGE

Age (years)	*Loading Dose*		*Maintenance Dose*		*Convalescent Dose*
	Severe	*Moderate*	*Severe*	*Moderate*	
0–1	500 mg.	400 mg	250 mg	200 mg	100 mg.
1–3	750 mg	500 mg	350 mg	300 mg.	150 mg
3–7	1 gm.	750 mg	500 mg.	350 mg.	200 mg.
7–12	1·5 gm	1 gm.	750 mg.	500 mg	250 mg.
12 and over	2–4 gm.	1·5 gm.	1 gm	750 mg	500 mg.

(For duration of treatment refer to section on specific infection)
(Interval—six-hourly.)

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Chapter VII

AUREOMYCIN

Aureomycin, derived from the fungus *Streptomyces aureofaciens*, is prepared for clinical use as the hydrochloride. Aureomycin hydrochloride possesses a therapeutic range which is similar to that of terramycin and exceeds that of other antibiotics at present in general use. Its range includes most Gram-positive and Gram-negative bacteria and all the rickettsiæ; in the treatment of diseases of virus origin it is superior to other available antibiotics Toxic manifestations are few and for the most part of little importance.

Pharmacology

The antibacterial effect of aureomycin against Gram-positive ... t of ... sto- ... pt-

ible to aureomycin than penicillin. Gram-positive cocci and *Corynebacterium diphtheriæ* are sensitive to concentrations of 0·1 μg. per ml. Staphylococci, which have become resistant to penicillin, retain their sensitivity to aureomycin. ...

few successes have been claimed, aureomycin is generally considered to be of little therapeutic value in infections caused by these two organisms.

In general, Gram-negative organisms are slightly less susceptible to aureomycin than to chloramphenicol. It is of interest that the *in vitro* activity of both drugs against *Salm. typhi* is of the same order, yet only chloramphenicol is effective in the treatment of typhoid fever.

...that of chloramphenicol and terra-

modes of action

Absorption.—Aureomycin is readily absorbed from the intestine, giving appreciable concentrations in the blood stream after about four hours. The administration of 1 gm by mouth gives a serum concentration of about 4 µg. per ml. from the fourth to twelfth hour. Although the level falls steadily thereafter, detectable amounts may persist for twenty-four hours.

Following intravenous injection of 0 5 gm., concentrations of about 14 µg. are rapidly reached.[2] The level falls, becoming about the same as that following oral administration at the twelfth hour. On these doses therapeutic blood levels will be maintained for six to twelve hours.

antibiotics carried to the organs and tissues by the blood stream, are mainly dependent on the blood supply Therapeutic concentrations are readily but slowly obtained in synovial, pericardial, pleural and peritoneal effusions; the drug levels reached are always lower than the corresponding levels in the blood, a fact which makes it necessary to employ the maximal dosage for the treatment of infections in these situations. Concentrations in the less vascular tissues, such as brain, bone and necrotic areas, are

intravenous injection of 0 5 gm. of aureomycin concentrations in

urine. Excretion in the bile is usually of little therapeutic value in cholecystitis and empyema of the gall bladder, as in these conditions the cystic duct is frequently obstructed. The concentration in the urine is roughly proportionate to that in the blood in the ratio of 100 : 1.[5] Hence even with small doses effective concentrations can be obtained in the urine.

Renal insufficiency diminishes the rate of excretion and gives rise to abnormally high and prolonged concentrations in the blood. By design, a similar result follows the administration of caronamide.

antibiotics, chloramphenicol and terramycin.[6] Those most commonly encountered are due to the drug's local action on the intestinal tract after oral administration. Hypersensitivity reactions are seen on occasion and also reactions resembling those due to avitaminosis B. Inhibition of intracellular metabolism of *the host has been shown to occur under experimental conditions.*

GASTROINTESTINAL DISTURBANCES AND ALTERATION OF FLORA

Oral administration of the drug may be accompanied by signs of intestinal disturbance—namely, nausea and less frequently vomiting and diarrhœa. Minor symptoms may be present in as many as 30 per cent. of the patients treated. The governing factors in causation appear to be the size of the individual doses and con-

may even be necessary to discontinue oral administration The choice then lies between the maintenance of therapy by the intravenous route or the replacement of aureomycin *by another* antibiotic (but not by chloramphenicol).

Aureomycin, when given by mouth, eradicates all sensitive organisms within the lumen of the intestine, causing almost com- ... odourless. Absence ... nthesis of ... ent signs, *which have been attributed to deficiency*, are a red sore tongue and stomatitis. Changes in the vaginal mucosa have also been reported.[8] Symptoms may appear as early as the fourth day, their ... the longer treatment is continued. Preventive ... *r a suitable substitute)* ... nt exceeds five days.

HYPERSENSITIVITY

Of no serious significance are the maculopapular, urticarial and

scarlatiniform skin rashes which have been reported. They may occur alone or in conjunction with other manifestations of hypersensitivity or with glossitis. Drug fever and vertigo have also been reported.[4] A severe idiosyncratic reaction has been recorded in a patient known to be sensitive to penicillin, which suggests that cross-sensitisation is possible.[7]

Herxheimer-like Reactions

Acute exacerbations in the severity of acute brucellosis have been reported when the antibiotic is commenced at full dosage. This reaction, as in typhoid fever treated with chloramphenicol, can be prevented by employing small doses for the first twenty-four hours. It is, however, usually mild and a low initial dosage is not routinely employed.[8]

Effect on Antibody Formation

Aureomycin in optimal dosage may, like penicillin, by cutting short the period of contact between pathogen and host interfere with the normal development of antibodies.[10] Thus, the complement-fixing antibodies in psittacosis and the cold agglutinins in atypical pneumonia may fail to appear.[4] As diagnosis frequently rests upon the finding of a rising titre of these substances in the blood, proof of diagnosis may be difficult in a successfully treated patient.

Effect on the Host's Cells

Lépine and his colleagues (1950) have tested the effect of aureomycin and chloramphenicol on the rate of proliferation of the cells of normal chick embryos. They find that concentrations of the drugs of the same order as those used for therapeutic purposes in man (10 to 1,000 γ per ml.) are inhibitory. Concentrations of 1,000 γ per ml. may even produce death of the cell.[11] The significance of this phenomenon in human medicine has not been explored.

Resistance

As the action of the antibiotic is suppressive rather than bactericidal, the emergence of resistant strains is theoretically possible. In the relatively short time of our experience with aureomycin, the incidence of acquired resistance has been low. In two patients with bacterial endocarditis caused by *Str. fæcalis* an increase of resistance of the organism has been demonstrated.[12] Another

report mentions acquired resistance by *Bact. coli* in a urinary tract infection.[4]

Administration

The high acidity of aureomycin restricts the possible routes of administration to the oral and intravenous. In view of the drug's ready diffusion throughout the various organs and tissues of the body, this is usually no disadvantage. It has, however, been found possible to inject buffered solutions into the lateral ventricles of the brain and into the spinal theca without ill effect. Ten mg. of aureomycin in 10 ml. of one sixth molar sodium lactate were employed for this purpose.[13]

For systemic infections of moderate severity the drug should be administered orally. The intravenous route is used to obtain a rapid effect in severe and fulminating infections, maintenance dosage being continued by the oral route. Intravenous injection may also become necessary if the patient is unable to take the capsules by mouth by reason of impaired consciousness, delirium, or vomiting.

When the antibiotic is given intravenously it must be diluted in 20 c.c. of sterile distilled water and injected slowly to avoid the risk of thrombophlebitis.

In infants under the age of six months the drug without a capsule can usually be administered by mouth, if mixed with feeds. At this age the intense bitter taste does not appear to be resented.

Under no circumstances should the preparation at present available for oral use be employed for injection, rectal or local administration.

Dosage

For the treatment of all infections it is recommended that an initial loading dose, either oral or intravenous, be used. This will be followed every four or six hours by a maintenance dose, usually oral, until the infection has been controlled

[illegible] the initial loading dose (oral)

severe infections the initial loading dose (oral) may be calculated on the scale of 20 mg. per pound for children and 15 mg. per pound for adults. If the intravenous route is chosen the dose

may be calculated on the basis of 10 mg. per pound, given at a single injection

The daily maintenance dose for children should be on the basis of 25 to 50 mg per pound, and for adults, of 15 to 25 mg. per [illegible] The intravenous [illegible] one-half of the [illegible]

The daily maintenance dose is given in parts four to six-hourly.[14]

AUREOMYCIN

Table of Dosage

Age (years)	Loading Dose		Maintenance Dose	
	Severe	Moderate	Severe	Moderate
0-1	400 mg.	200 mg	200 mg	125 mg
1-3	500 mg	300 mg	300 mg	200 mg
3-7	600 mg	400 mg	400 mg	250 mg
7-12	750 mg	500 mg	500 mg	300 mg
12 and over	1-1 5 gm	750 mg	750 mg	500 mg

(Interval—six-hourly)
(For duration of treatment refer to section on specific infection)

Further experience of the treatment of infections with aureo- [illegible]

[illegible] be stopped are considered for each infection elsewhere. In acute infections treatment will be continued until the temperature has remained normal for forty-eight hours, or in chronic infections until the maximal benefit has been obtained and the risk of relapse is slight. This may be four to six weeks or even longer

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report mentions acquired resistance by *Bact. coli* in a urinary tract infection.[4]

ADMINISTRATION

The high acidity of aureomycin restricts the possible routes of administration to the oral and intravenous. In view of the drug's ready diffusion throughout the various organs and tissues of the body, this is usually no disadvantage. It has, however, been found possible to inject buffered solutions into the lateral ventricles of the brain and into the spinal theca without ill effect. Ten mg. of aureomycin in 10 ml. of one sixth molar sodium lactate were employed for this purpose.[13]

For systemic infections of moderate severity the drug should be administered orally. The intravenous route is used to obtain a rapid effect in severe and fulminating infections, maintenance dosage being continued by the oral route. Intravenous injection may also become necessary if the patient is unable to take the capsules by mouth by reason of impaired consciousness, delirium, or vomiting

When the antibiotic is given intravenously it must be diluted in 20 c.c. of sterile distilled water and injected slowly to avoid the risk of thrombophlebitis.

In infants under the age of six months the drug without a capsule can usually be administered by mouth, if mixed with feeds. At this age the intense bitter taste does not appear to be resented.

Under no circumstances should the preparation at present available for oral use be employed for injection, rectal or local administration.

DOSAGE

[illegible]

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may be calculated on the basis of 10 mg per pound, given at a single injection.

The daily maintenance dose for children should be on the basis of 25 to 50 mg. per pound, and for adults, of 15 to 25 mg per [illegible] The intravenous [illegible] one-half of the

The daily maintenance dose is given in parts four to six-hourly.[14]

AUREOMYCIN

Table of Dosage

Age (years)	Loading Dose		Maintenance Dose	
	Severe	*Moderate*	*Severe*	*Moderate*
0–1	400 mg.	200 mg	200 mg.	125 mg
1–3	500 mg	300 mg	300 mg	200 mg
3–7	600 mg.	400 mg	400 mg	250 mg.
7–12	750 mg	500 mg	500 mg	300 mg
12 and over	1–1·5 gm.	750 mg	750 mg	500 mg

(Interval—six-hourly.)
(For duration of treatment refer to section on specific infection.)

Further experience of the treatment of infections with aureomycin will no doubt lead to modifications of the standard schedules of dosage. In fulminating infections higher doses than those quoted may be given safely. The factors which decide that treatment shall be stopped are considered for each infection elsewhere. In acute infections treatment will be continued until the temperature has remained normal for forty-eight hours, or in chronic infections until the maximal benefit has been obtained and the risk of relapse is slight. This may be four to six weeks or even longer.

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Chapter VIII

TERRAMYCIN

TERRAMYCIN is an antibiotic produced by the fungus *Streptomyces rimosus*, and is prepared as an amphoteric crystalline substance, whose salts are soluble in water and stable to heat.

The antibacterial and antiviral activity and side effects resemble closely those of the allied antibiotics, aureomycin and chloromycetin Preliminary clinical trials leave little doubt that it is a potent and useful antibiotic, though insufficient time has elapsed since its discovery to allow its precise value to be estimated

STORAGE

The dry compound retains its potency for at least one year. In solution at refrigeration temperature potency is maintained for about three days.

PHARMACOLOGY

Terramycin possesses a powerful action against Gram-positive and Gram-negative bacteria, against rickettsiæ and the larger viruses. In general the *in vitro* activity against Gram-positive organisms is similar and against Gram-negative organisms and *Ps pyocyanea* somewhat superior to that of aureomycin It further resembles aureomycin in its poor effect against *Proteus vulgaris* and *Salm. typhi*, but differs by possessing a small but definite effect against *Myc. tuberculosis.*

Str. pyogenes, viridans streptococci, pneumococci, *B. subtilis*, most strains of *Staph. aureus* and *Staph. albus*, *Str. fæcalis*, meningococci, gonococci, *Trep. vincenti*, *C diphtheriæ*, *B. anthracis*, *Actinomyces bovis*, *Bact. coli*, *Bact aerogenes*, *Bact friedländeri*, *H. pertussis*, *H. influenzæ*, salmonellæ, dysentery organisms, *Past. pestis*, *Br. tularense*, *Trep. pallidum*, *Trep. recurrentis* and *Trep pertenue* are sensitive, commonly to concentrations between 0·1 and 7 µg per ml.[1,2] A few strains of *Staph. aureus*, *Bact. coli*, *Bact. aerogenes* and viridans streptococci, however, show marked insensitivity.[2] During therapy resistant hæmolytic staphylococci

have been found to replace the normal flora of the sputum in a proportion of patients.[3]

Terramycin is ineffective against fungi and the viruses of measles, smallpox, chicken pox and mumps, but inhibits intestinal amœbæ, including *Entamœba histolytica*.[4]

Absorption.—Following oral administration, the antibiotic is detectable in the blood within one hour. Single doses of 0·5 to 1·25 gm give therapeutic blood concentrations of 0·5 to 8 μg. per ml. which are maintained for at least six hours and are often detectable for as long as twenty-four hours. Single doses greater than 1 gm. are reported not to give rise to proportionately higher levels in the blood or urine, the surplus antibiotic passing unabsorbed in higher concentration in the fæces.[5] In small children and infants relatively higher dosage is probably necessary to produce blood concentrations comparable to those attained in adults.

Diffusion.—Terramycin diffuses readily into the pleural and peritoneal fluids and partially into the fœtal circulation.[6] There is uncertainty regarding the quantity which reaches the cerebrospinal fluid. Diffusion into the vascular tissues of the body gives adequate concentrations, which are of the same order as those obtained with chloramphenicol and aureomycin.

Excretion.—Terramycin is concentrated and excreted both by [illegible] excreted in a biologically active form.

Toxicity.—The toxicity of terramycin is low and, like aureomycin and chloramphenicol, the most common reaction is gastrointestinal disturbance, characterised by looseness of the bowels and occasionally nausea and vomiting.

These effects are seen particularly with high doses given on an empty stomach. Glossitis, stomatitis, and sensitisation reactions have also been reported, and rarely may be sufficiently severe to warrant stopping treatment.[3]

Resistance

By *in vitro* experiments it has been possible to increase the resistance of certain organisms to terramycin.[2] Resistance to terramycin appears to be of the "penicillin" rather than of the "streptomycin" type and thus resembles that to aureomycin and chloramphenicol.

ADMINISTRATION

Terramycin is administered by the oral route as a capsule or elixir. For intravenous injection, which may be employed for rapidity of effect or when oral administration is contraindicated, the antibiotic must be diluted in at least 100 ml. of sterile distilled water, saline or 5 per cent. dextrose The rate of injection should not exceed 100 ml. in five minutes, owing to the danger of thrombophlebitis. Thus it is often convenient to employ a continuous drip infusion. As soon as the patient's condition permits the oral route should be adopted. Local injection into walled-off abscess cavities may be performed, so long as care to avoid leakage into the adjacent tissues is exercised. Subcutaneous and intramuscular injections are contraindicated. Ointments for ophthalmic use (containing 1 mg. terramycin per 1 gm. of base) and for topical use (containing 30 mg. terramycin per 1 gm) are prepared

DOSAGE

The most effective dosage of terramycin has not yet been established, but the following is believed to be adequate in the light of present knowledge for the majority of infections. An initial oral loading dose, equal to twice the maintenance dose, is recommended in the treatment of acute infections, followed by an oral maintenance dose on the basis of 25 mg. per kilogram (2 2 lb) of body weight every six hours. This régime should be continued until the patient has been apyrexial for at least forty-eight hours. The intravenous dose for adults is, depending on the severity of the infection, 0 5 to 2 gm daily (2 gm should not be exceeded).

The oral maintenance dose for infants and children below the age of five should be on the basis of 50 mg per kilogram (2 2 lb), or 25 mg. per lb. of body weight, six-hourly, with a loading dose of twice this amount.[7]

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Chapter IX

CARDIOVASCULAR DISEASES

Prophylaxis of Rheumatic Fever and Bacterial Endocarditis

ORGANISMS: Streptococci

DRUGS OF CHOICE AND DOSES

(1) **Penicillin:** (*a*) as a prophylactic measure to cover tonsillectomy and dental extraction. 300,000 units of crystalline penicillin twelve-hourly for four days, or procaine penicillin 300,000 units daily; intramuscular.

(*b*) Procaine penicillin 600,000 units every third day throughout autumn and winter months; intramuscular. (For prophylaxis of relapses and endocarditis.)

(2) **Sulphadimidine, Sulphadiazine:** 0·5 gm. twice daily, throughout autumn and winter months.

(See remarks concerning toxicity and the precautions necessary on page 16.)

CHOICE OF DRUG.—Penicillin is preferred as the prophylactic agent for surgical procedures. For winter prophylaxis the principal advantage of penicillin lies in the absence of toxicity. It has the disadvantage that injections are necessary over a long period and in comparison with sulphonamides it is costly.

SPECIAL CONSIDERATIONS

(1) **Preliminary Freedom from Infection.**—Before the winter prophylactic régime is instituted, throat and nose swabs must be negative for streptococci. If prophylaxis is started in the presence of streptococci, they may not be eradicated and resistant strains will emerge. Thus no protection is afforded to the patient.

(2) **Tonsillectomy—Dental Extractions.**—In patients with valvular lesions of the heart, intramuscular therapy should be commenced forty-eight hours before operation and continued for a similar period after operation.

(3) **Masking of the Clinical Features of Rheumatic Fever.**—During prophylaxis, joint involvement may be manifest

and the patient or his parents are aware of their significance

leucocyte count should be made weekly from the second to eighth week and repeated on the occurrence of a sore throat or fever. The patient must be impressed with the importance of reporting immediately if these symptoms appear

(5) **Streptococcal Infections.**—Rheumatic subjects should receive systemic penicillin in therapeutic doses without delay for acute sore throats presumed to be streptococcal on the clinical appearances. (Throat swabs should be taken)

RESULTS OF PROPHYLAXIS

(1) **Rheumatic Fever.**—The incidence of streptococcal infections can be lowered, but not altogether abolished, by prophylaxis. When infection is present, however, it is doubtful if antibiotics are of any value in preventing rheumatic fever.[1,2]

In view of this doubt it is preferable to offer penicillin prophylaxis to those who have recently had rheumatic fever, rather than to treat established infections. The chief hazard of prophylaxis is the frequency with which acquired resistance is encountered.

(2) **Bacterial Endocarditis.**—Dental extractions and tonsillectomy may be undertaken without risk of causing bacteræmia, and therefore with safety, in patients suffering from valvular disease of the heart.

Bacterial Endocarditis

SUBACUTE BACTERIAL ENDOCARDITIS

CAUSATIVE ORGANISMS. (1) Viridans streptococci
(2) *Str fæcalis*

1. Viridans streptococci

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (crystalline)· 2-10,000,000 units daily, in six doses, intramuscular, for at least six weeks.

ing during treatment, are easily overlooked. Their presence will demand special treatment, as described elsewhere.

RESULTS OF TREATMENT.—Although the numbers of such cases treated are few, it appears that the mortality rate remains high under the most favourable circumstances. The recovery rate of pneumococcal endocarditis is given as 40 per cent., of hæmolytic streptococcal endocarditis 50 per cent., and of staphylococcal endocarditis 20 per cent.[6]

Cardiovascular Syphilis

CAUSATIVE ORGANISM: *Trep. pallidum*

DRUGS OF CHOICE AND DOSES

(1) **Potassium iodide:** 5 grains t.d.s.
Liquor hydrargyri perchloridi: *1 drachm b.d. followed by:*
(2) **Bismuth metal** (or bismuth oxychloride): 0·2 gm. weekly, intramuscular, for six weeks; followed by:
(3) **Penicillin:** 100,000 units four-hourly, or procaine penicillin 600,000 units daily, intramuscular, for twelve to fourteen days; followed by a second course of bismuth for three months with neoarsphenamine.
(4) **Neoarsphenamine:** 0·3 gm. weekly; intravenous; five-week course.

CHOICE OF DRUG.—While penicillin is the more active drug, [illegible] should be employed in the first instance as [illegible] tment [illegible] using untoward reactions.

SPECIAL CONSIDERATIONS

(1) **Limitations of Anti-spirochætal Drugs.**—The aim of treatment of established aortitis should be to prevent further damage by arresting the infective process. Secondary fibrosis and [illegible] pathological changes, are, [illegible]

Positive serological reactions are unreliable indicators of activity, and conversion, while desirable, should not be the sole aim of treatment. [illegible]

penicillin after giving a preliminary course of iodides and mercurials.[8]

(3) **General Measures.**—The established routine of management of patients suffering from cardiovascular syphilis must be maintained. The intensity of specific treatment, especially with arsenicals, should be varied according to the severity and stage of the disease.

CRITERIA OF CURE.—Complete cure of the disease cannot be expected and reliance should not be placed on conversion of the serological reactions. In general, courses of treatment should be given until no further symptomatic improvement takes place.

RESULTS OF TREATMENT.—There is little doubt that penicillin is capable of checking the infection in many cases, but it is yet too early to make a final assessment of its value. Iodides, mercurials and general cardiac measures alone will do much to relieve pain.

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CHOICE OF DRUG.—Penicillin remains the most potent dr available, and is preferred to aureomycin and sulphonamide In infancy and in patients over 40 years of age aureomycin terramycin by reason of their wider range against pulmona flora of relatively low pathogenicity may become the drugs choice. At the present time penicillin with a sulphonamide shoul be given in these age groups.

SPECIAL CONSIDERATIONS

The remarks concerning general measures, physiotherapy an the occurrence of complications in lobar pneumonia apply wit even greater force to the management of patients suffering fro *bronchopneumonia*.

(1) **Secondary Bronchopneumonia.**—Bronchopneumonia i frequently a complication of other diseases, such as measles, per tussis, bronchiectasis, virus influenza, polycystic disease an pulmonary hypostasis. In these diseases prevention must alway be the ideal. Appropriate treatment of the original conditio where possible must be instituted in addition to chemotherapy.

(2) **Delayed Resolution.**—Resolution must be assisted b more intensive breathing exercises and postural coughing for te *minutes four times daily. If improvement is not apparent in si* weeks bronchoscopy should be considered

CRITERIA OF CURE.—The same criteria as for lobar pneumoni will be used in deciding to discontinue chemotherapy.

RESULTS OF TREATMENT.—Bronchopneumonia carries a hig mortality in spite of modern therapeutic agents, for it is essentially a disease of those with a low resistance. Clinical trials wit aureomycin would suggest that it may be the most effective antibiotic in lowering the mortality in old age.[2]

Staphylococcal Pneumonia

CAUSATIVE ORGANISM: *Staphylococcus aureus*

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose): 500,000 to 1,000,000 units depending on bacterial sensitivity, four-hourly; intramuscular.
(For details of dosage see page 34.)

(2) **Aureomycin** (adult dose): Loading 1·5 gm.; *maintenance* 1 gm., six-hourly; oral.
(For details of dosage see page 57.)

(3) **Streptomycin** (adult dose): 1 to 1·5 gm. twice daily.
(For details of dosage see page 41. For limitations of toxicity and resistance see page 37.)

(4) **Sulphadimidine** (adult dose): Loading 3 to 6 gm.; eight hours 1·5 to 3 gm. four-hourly; maintenance 1·5 four-hourly.
(Alternatives: sulphathiazole, sulphadiazine.)
(For details of dosage see page 21. For details of durat and toxicity see page 16.)
(See note below concerning potency.)

CHOICE OF DRUG.—Penicillin is the most effective antibiot except in cases due to resistant organisms. Where the degree resistance is small, larger doses of penicillin may still be therapeutic. Where the degree of resistance is high, aureomycin should be given. Chloramphenicol, streptomycin and sulphonamides are less powerful against penicillin-resistant staphylococci and have been largely superseded by aureomycin. Streptomycin and sulphonamides should be used in conjunction with other drugs, as they are not sufficiently potent to be relied upon if given alone.

SPECIAL CONSIDERATIONS

(1) **Lung Abscess.**—Staphylococcal pneumonia, whether a local manifestation of a staphylococcal septicæmia or an infection secondary to other vascular or neoplastic conditions or an apparently isolated lesion, runs a natural course ending in necrosis and lung abscess. These lung abscesses may have the radiological appearance of cysts in the lung. The aim of treatment must be to check the infection before necrosis of lung tissue takes place. Hence antibiotic treatment must be instituted without delay and in high dosage. While awaiting the results of bacteriological investigations, it is recommended that treatment be commenced with a combination of drugs, so that if the organism proves to be insensitive to one, time will not have been lost. In established lung abscess the specific measures outlined in the section on lung abscess may become necessary.

(2) **Primary Focus.**—A primary staphylococcal lesion—e.g., osteomyelitis or mastoiditis—must be sought and, if present, suitably treated.

(3) **Bacterial Sensitivity.**—Estimation of the degree of sensitivity of the infecting organism to penicillin is imperative. At the same time it is important to estimate the degree of sensitivity to aureomycin, streptomycin and sulphonamides.

(4) **Physiotherapy.**—Physiotherapy, as already described for pneumococcal pneumonia, is an important adjunct in the management of staphylococcal pneumonia.

CRITERIA OF CURE.—The duration of treatment is determined by the same principles as for other pneumonias. It will be continued until the patient has been apyrexial for at least seventy-two hours and until primary or metastatic foci have healed.

RESULTS OF TREATMENT.—With early diagnosis and prompt

Friedländer Pneumonia

CAUSATIVE ORGANISM: *Bact. friedländeri* (*Klebsiella pneumoniæ*)

DRUGS OF CHOICE AND DOSES

(1) **Streptomycin** (adult dose): 1 gm. twice daily; intramuscular.
(For details of dosage see page 41.)

(2) **Polymyxin** (adult dose): 25-50 mg. four-hourly; intramuscular.
(For details of dosage see page 45.)

(3) **Aureomycin** (adult dose): Loading 1·5 gm., maintenance 1 gm. six-hourly; oral.
(For details of dosage see page 57.)

(4) **Chloramphenicol** (adult dose): Loading 1·5 gm, mainten-

(5) [illegible] -eight hours
1·5 gm. four-hourly, maintenance 1 gm. four-hourly; oral.
(For details of dosage see page 21. For details of duration and toxicity see page 16.)

CHOICE OF DRUG.—Streptomycin is the most firmly established [illegible]

although at the present time the number of cases treated is too small for their true value to be estimated. Experimentally, the *most potent agent is polymyxin,*[3,4] which has been employed *successfully in the human disease.*[5]

Bacterial sensitivity to the range of drugs should be estimated at the start of treatment, so that the most effective agent may be chosen and the dose correctly adjusted without delay.

The probability that strains resistant to streptomycin will emerge substantially increases when streptomycin alone is continued in the absence of a favourable response for longer than ten days The response, when it occurs, will usually be apparent within four to five days. If, therefore, improvement has not commenced within five days, treatment must be reviewed in the light of drug sensitivity.

SPECIAL CONSIDERATIONS

Abscess Formation.—The natural course of Friedländer pneumonia is towards necrosis and abscess formation. It is, therefore, imperative that there is no delay in starting intensive treatment.

[illegible]

recovery from the acute infection is incomplete.[8]

Influenzal Pneumonia

CAUSATIVE ORGANISM: Pfeiffer's bacillus (*Hæmophilus influenzæ*)

DRUGS OF CHOICE AND DOSES

(1) **Streptomycin** (adult dose): 1 gm twice daily; intramuscular.
(For details of dosage see page 41. For limitations due to

[illegible]

1 gm. four-hourly.
(For details of dosage see page 21 For limitations due to toxicity see page 16.)

(2) **Aureomycin** (adult dose). Loading dose 1 5 gm, maintenance 1 gm six-hourly, oral.
(For details of dosage see page 57)

(3) **Polymyxin** (adult dose): 25-50 mg four-hourly; intramuscular.
(For details of dosage see page 45)

(4) **Chloramphenicol** (adult dose): Loading 1·5 gm., maintenance 1 gm four-hourly; *oral.*
(For details of dosage see page 50.)
(5) **Penicillin** (adult dose): 300,000 units four-hourly.

is at present the accepted treatment. Recent work with aureomycin, polymyxin and chloramphenicol in the treatment of *H. influenzæ* meningitis gives hope that these agents may also be of value in the treatment of the pulmonary infection [7,8,9,10] Penicillin in combination with sulphadiazine is not so effective as streptomycin and *sulphadiazine and should no longer be relied upon.*

SPECIAL CONSIDERATIONS

The same need for breathing exercises and postural coughing during the stage of recovery exists as for lobar pneumonia (page 68).

CRITERIA OF CURE.—Specific therapy may be stopped when the patient's temperature returns to normal in favourable cases. If the response has been slow, continuation of therapy for a further two days is advisable.

RESULTS OF TREATMENT.—Sufficient numbers of patients have not yet been treated to enable an evaluation of the newer antibiotics to be made.

Virus Pneumonia

CAUSATIVE ORGANISMS: Virus of atypical pneumonia
[Virus of psittacosis (see page 127)]
[*Rickettsia burneti* (Q fever) (see page 127)]

DRUGS OF CHOICE AND DOSES

(1) **Aureomycin** (adult dose): Loading 1 gm., maintenance 0·5 to 1 gm. six-hourly; oral.
(For details of dosage see page 57.)
(2) ***Chloramphenicol*** (adult dose) Loading 1 gm, maintenance 0·5 to 1 gm, four-hourly; oral.
(For details of dosage see page 50.)

CHOICE OF DRUG.—*Aureomycin and chloramphenicol are on* present evidence considered to be of similar efficacy in atypical pneumonia and either may be prescribed.

SPECIAL CONSIDERATIONS

In psittacosis the pulmonary lesions are manifestations of a virus septicæmia As in typhoid fever, general measures and symptomatic treatment will be required

[illegible]

and the temperature has remained normal for at least forty-eight hours.

(2) **Psittacosis and Q Fever.**—As relapses after stopping aureomycin therapy are encountered, antibiotic treatment should be continued until the patient has been apyrexial for at least three days The minimal safe duration of treatment has not been established.

RESULTS OF TREATMENT —In atypical pneumonia and Q fever the results of treatment are good and rapid recovery is the [illegible]

[illegible]

what extent recovery is hastened and mortality reduced

Lung Abscess

CAUSATIVE ORGANISMS *Staphylococcus aureus*
Bact. friedländeri (*Klebsiella pneumoniæ*)
Streptococcus pyogenes
Fusiform bacilli and spirilla
Other bronchial flora

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose) 1,000,000 to 2,000,000 units (depending on sensitivity) twice daily, intramuscular
(For details of dosage see page 34)
(2) **Aureomycin** (adult dose) Loading 1 5 gm., maintenance 1 5 gm , six-hourly, oral
(For details of dosage see page 57)
(3) **Sulphadimidine, sulphadiazine** (in conjunction with an antibiotic) (adult dose) Loading 4 gm , first forty-eight hours 2 gm., four-hourly, maintenance 1 5 gm , four-hourly, oral.
(For details of dosage see page 21 For limitations and toxicity see page 16)

(4) **Streptomycin** (adult dose): 2 gm., twice daily, intramuscular (sulphadiazine to be given also).
(For details of dosage see page 41. For limitations due to toxicity and resistance see page 37.)

(5) **Polymyxin** (adult dose): 25 gm. four-hourly; intramuscular.
(For details of dosage see page 45.)

CHOICE OF DRUG.—The great majority of infections are caused

infecting organism is only partially sensitive in higher doses, is the drug of choice. Aureomycin, streptomycin, polymyxin and sulphonamides may be required for the more rare infections due to *Bact. friedländeri*, *H. influenzæ*, etc., and with the exception of polymyxin, for penicillin-resistant staphylococcal infections.

SPECIAL CONSIDERATIONS

(1) **Bacteriological Diagnosis.**—It is imperative to obtain complete information regarding the infecting organism or organisms and their drug sensitivities, at the outset.

(2) **Bronchoscopy.**—The greatest value of bronchoscopy lies in diagnosis and investigation rather than treatment. In treatment it may be required for the establishment of drainage.

(3) **Prompt and Intensive Chemotherapy.**—Early chemotherapy in adequate dosage is the most important measure for both prophylaxis and treatment.

(4) **Postural Drainage.**—Postural drainage according to the anatomical localisation of the abscess is necessary to permit evacuation of pus and debris; it should be given for as long a period as the patient can tolerate at a time.

CRITERIA OF CURE.—Antibiotics will be necessary for several weeks, until purulent sputum ceases, the patient is apyrexial, the leucocyte count is normal, and there is radiological evidence of healing.

RESULTS OF TREATMENT.—Postural drainage and systemic peni-

Empyema

CAUSAL ORGANISMS: Any organism capable of causing pneumonia may be the causal organism of empyema·
Streptococcus pyogenes
Pneumococci (*Str. pneumoniæ*)
Staphylococcus aureus
Bact. friedländeri (*Klebsiella pneumoniæ*)
Viridans streptococci

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose): (*a*) Intramuscular, 1,000,000 to 2,000,000 units, twice daily. (*b*) Intrapleural, 100,000 units in 5 ml. normal saline daily.
(2) **Aureomycin** (adult dose): Loading 1 5 gm., maintenance 1 gm six-hourly; oral
(For details of dosage see page 57.)
(3) **Streptomycin** (adult dose): 1 gm. twice daily; intramuscular.
(For details of dosage see page [illegible])

(4) [illegible] -eight hours 1·5 to 2 gm. four-hourly, maintenance 1·5 gm. four-hourly, oral.
(5) **Sulphadimidine** (adult dose). Loading 3 to 6 gm, first forty-eight hours 1·5 gm. four-hourly, maintenance 1 gm. four-hourly; oral.
(For details of dosage see page 21. For limitations due to toxicity see page 16.)

CHOICE OF DRUG.—The choice of drug will finally depend on the nature of the pathogen and the laboratory information regarding its drug sensitivity.

For the majority of empyemata, caused by pneumococci or *Staph. aureus*, penicillin is the drug of choice. Aureomycin or streptomycin with penicillin or sulphadiazine are preferred for penicillin-resistant staphylococcal infections. Polymyxin or streptomycin with sulphadiazine may be employed for the rare infections by susceptible Gram-negative organisms, such as *Bact. friedländeri*.

SPECIAL CONSIDERATIONS

(1) **Local Therapy.**—Intrapleural injection of penicillin is indicated for all those due to susceptible pathogens, but not for sterile post-pneumonic empyemata

(2) **Aspiration.**—Aspiration of the chest will be performed, *daily or on alternate days, before injecting penicillin to avoid* undue dilution. The quantity removed will be decided by the volume and rate of reaccumulation of fluid, the toxæmia of the *patient and the need for relief of dyspnœa.*

(3) **Breathing Exercises.**—As soon as infection has been controlled, breathing exercises should be instituted, in order to *aid re-expansion of the lung and to prevent fixity and deformity of* the chest.

(4) **Surgery.**—Surgical evacuation becomes necessary if im-*provement is prever* [illegible]

(5) **Post-pneum** [illegible]
follow pneumonia, [illegible]
sterile. Repeated intrapleural injection is therefore unnecessary.

Criteria of Cure.—Intrapleural therapy may be discontinued when the fluid has become sterile and no new exudate is formed, *which usually occurs in two to four weeks. Systemic therapy will* [illegible]

[illegible]

cent.[13] Although chronic empyemata are more commonly seen in adults than in children, a similar improvement in prognosis has *taken place.*

Bronchiectasis

Causative Organisms: Indeterminate bronchial flora

(The pathogenesis of bronchial dilatation is considered to be in part due to obstruction of the bronchi and in part to infection.)

Drugs of Choice and Doses

(1) **Penicillin** (adult dose): Intramuscular, 600,000 units twice daily.
(For details see page 34.)
Inhalation: 100,000 units in 5 *ml.* of normal *saline, four* times daily—by suitable inhaler.

(2) **Streptomycin** (adult dose): 1 to 2 gm. daily; intramuscular.

Choice of Drug.—*At present penicillin is the most generally* useful antibiotic, but it seems probable that aureomycin and terramycin may find places in treatment, in view of their powerful action *against nearly all bronchial organisms,* including those insensitive to penicillin.

SPECIAL CONSIDERATIONS

(1) **Postural Drainage and Surgery.**—Penicillin therapy (in courses of seven days) should be employed for the control of acute exacerbations and thus indirectly for the prevention of extension of the disease to adjacent segments of the lung. Thorough postural drainage, and in suitable cases excision of the affected segments or lobes, remain the basic methods of treatment. Combination of penicillin with streptomycin is recommended where the infecting organism is relatively insensitive to penicillin and in mixed infections.

(2) **Penicillin Inhalation.**—Courses of inhalation therapy may be employed by the patient at home for the prevention and treatment of exacerbations and reduction of the volume of sputum. Little advantage is gained by continuing this form of treatment for longer than a week at a time

RESULTS OF TREATMENT.—Antibiotic therapy is usually effective in controlling acute exacerbations of infection, provided that adequate drainage is maintained and that resistant organisms do not preponderate. Inhalation of penicillin is temporarily effective in reducing toxæmia and the amount of sputum and is of special use to the patient in his home.

Bronchitis

CAUSATIVE ORGANISMS: Indeterminate bronchial flora

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose). 300,000 units four-hourly; intramuscular.
(For details of dosage see page 34.)

(2) **Sulphadimidine** (adult dose): Loading 3 gm., maintenance 1·5 gm. four-hourly.
(Alternatives: sulphadiazine, sulphamerazine. For details of dosage see page 21. For limitations due to toxicity see page 16.)

CHOICE OF DRUG.—Penicillin and sulphonamides are of approximately equal efficacy in the treatment of bronchitis, and either may be employed.

SPECIAL CONSIDERATIONS

(1) **Indications for Chemotherapy.**—Treatment with antibiotics is required only in the more severe cases of acute bronchitis,

collapse caused by plugs of tenacious secretion fails to improve rapidly in spite of adequate physiotherapy.

CRITERIA OF CURE.—Cure cannot be assumed until full re-expansion of the lung has taken place. Chemotherapy may be discontinued when fever has subsided and sputum has disappeared.

RESULTS OF TREATMENT.—Antibiotic therapy, if prompt, is nearly always effective in controlling infection. By this means it assists in reopening the airways, thus probably reducing the incidence of complications, such as lung abscess, bronchopneumonia and bronchiectasis.

Prophylaxis of Post-operative Chest Infections

CAUSATIVE ORGANISMS: Bronchial flora

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose): 300,000 units twice daily; intramuscular.
(For details see page 34.)
(2) **Aureomycin** (adult dose): Loading 0 75 gm, maintenance 0 5 gm. six-hourly; oral.
(For details see page 57.)

CHOICE OF DRUG.—Penicillin as the crystalline or aqueous procaine compound is the drug preferred for prophylaxis. Aureomycin and terramycin are now being employed with increasing frequency, as their range covers not only the bronchial flora but also the majority of pathogens complicating wound, intestinal and genito-urinary surgery.

SPECIAL CONSIDERATIONS

(1) **Prophylaxis for Surgical Procedures.**—Antibiotic therapy may be instituted at the time of operation when post-operative chest infection is anticipated. It is preferable to postpone operation if infection is already present, until the infection has been brought under control, but therapy must be started as early as possible if, as frequently happens, delay is impracticable. It is of great importance to make full use of pre-operative and post-operative breathing exercises.

(2) **Duration of Treatment.**—Prophylactic treatment may be discontinued three days after operation. If infection is present,

full dosage must be given until the patient has been afebrile for at least forty-eight hours.

RESULTS OF TREATMENT.—The results of treatment and pro- [illegible]

post-operative complications

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[illegible] F R, [illegible] 63
[illegible] H. B., [illegible]

Chapter XI

INFECTIONS OF THE UPPER RESPIRATORY TRACT

Streptococcal Infections of the Throat

CAUSATIVE ORGANISM: *Streptococcus pyogenes*

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose): 3-500,000 units twelve-hourly, intramuscular, or for maintenance procaine penicillin 3-500,000 units daily for three days.
(For further details see page 34.)

(2) **Sulphadimidine** (adult dose): Loading 3 to 4 gm., maintenance 1·5 gm. four-hourly; oral.
(Alternatives: sulphadiazine, "Sulphatriad," sulphamerazine.)
(For details of dosage see page 21. For details of toxicity see page 16.)

CHOICE OF DRUGS.—For the treatment of uncomplicated tonsillitis, penicillin is superior to sulphonamides, but the latter may be preferred on the grounds of economy and convenience. Penicillin should be given when a rapid antibacterial effect is essential, as, for instance, in tonsillitis occurring in rheumatic and nephritic patients.

Local application of penicillin by spray or lozenge is inadequate and is not to be recommended.

SPECIAL CONSIDERATIONS

(1) ***Masking of Diphtheria.**—As in the past, the precaution of taking a throat swab must never be overlooked in a patient with faucial exudate. Penicillin rapidly eradicates diphtheria* [illegible]

whose resistance is lowered or for whom streptococcal infection carries a special risk.

(3) **Recurrent Sore Throats.**—Recurrent attacks, other than those caused by reinfection, are commonly due to persistent infection in tonsils whose functions are impaired by the damage of earlier infections. In this case tonsillectomy is the rational treatment and antibiotics are of value only for the control of acute exacerbations.

(4) **Symptomatic Measures.**—Relief of pain, attention to the diet and fluid intake form the basis of routine medical treatment, whether antibiotics are employed or not.

RESULTS OF TREATMENT.—Streptococcal sore throat is a self- [illegible]

failure of treatment is usually due to inadequate dosage, errors in diagnosis, a resistant organism or foci of infection inaccessible to drugs.

Quinsy

CHOICE OF DRUG.—Penicillin is more effective in the presence of pus than are the sulphonamides and is, therefore, the antibiotic of choice in the treatment of quinsy.

SPECIAL CONSIDERATION

Surgical Drainage.—Drainage may be required in accordance with general surgical principles and for the relief of pain. Tonsillectomy performed during the acute phase, in conjunction with penicillin therapy, is a relatively safe and effective procedure in selected cases

CRITERIA OF CURE.—Penicillin should be continued until the patient has been afebrile and free of symptoms for forty-eight hours.

Retropharyngeal Abscess, Parapharyngeal Abscess and Ludwig's Angina

CAUSATIVE ORGANISM: *Streptococcus pyogenes*
(Rarely other organisms)

DRUG OF CHOICE AND DOSE

Penicillin (adult dose): 500,000 units twelve-hourly; intramuscular.

SPECIAL CONSIDERATIONS

(1) **Surgical Drainage.**—Localised pus will be drainec gically without delay, penicillin therapy being continued least forty-eight hours after operation.

(2) **Carotid Ligation.**—Epistaxis or other premor [illegible]

essential.

CRITERIA OF CURE.—Systemic therapy must be continued the patient has been afebrile for forty-eight hours and until of active infection have resolved.

RESULTS OF TREATMENT.—Excellent results follow adec treatment of early infections; extension of infection, abscess fo tion and complications are prevented. When an abscess is pre antibiotics may prevent extension, and after surgical drai increase the rate of healing.

Vincent's Angina

CAUSATIVE ORGANISM: Vincent's spirillum (*Trep. vincenti*) anc fusiform bacillus

DRUG OF CHOICE AND DOSES

Penicillin: (i) (adult dose): loading 300,000 units, twelve-hou intramuscular.

(*ii*) *100,000 units in 2 c.c. of water, three times daily,* spray.

SPECIAL CONSIDERATIONS

Systemic therapy forms the basis of treatment, and may supplemented by local application. The latter method, thou *often effective in minor infections,* is not recommended as sole method of treatment for moderate or severe infections.

[illegible] ms and healing [illegible] rule treatmen

RESULTS OF TREATMENT.—Penicillin is effective in most instanc bringing about rapid and complete recovery.

Sinusitis

CAUSATIVE ORGANISMS: Nasal flora (streptococci, pneumococci, staphylococci)

DRUGS OF CHOICE AND DOSE

(1) **Penicillin:** (i) (adult dose) 300,000 units twelve-hourly; intramuscular.
(ii) Instillation of 200,000 units in 2 c c of water.

(2) **Sulphadiazine** (adult dose): Loading 2 gm, 1 5 gm. four-hourly for forty-eight hours, 1 gm four-hourly for three to five days; oral

(For details regarding toxicity see page 16.)

(Alternatives sulphadimidine, sulphamerazine, "Sulphatriad.")

CHOICE OF DRUG.—Penicillin, having a wider range and greater potency against respiratory pathogens in purulent exudates, is preferred to the sulphonamides. In all severe acute lesions the antibiotic should be injected intramuscularly. Nasal instillation of sulphacetamide is widely used and is often beneficial in mild infections.

SPECIAL CONSIDERATIONS

(1) **Limitations.**—Antibiotics are valuable adjuncts to the treatment of acute sinusitis, but bring little if any benefit in chronic infections Except as a cover for surgery and to control exacerbations they have no place in the management of the latter condition

(2) **Aeration and Drainage.**—In all forms of sinusitis the re-establishment of aeration and drainage by medical, physical or surgical means remain of first importance and are indispensable to success in any scheme of treatment.[3]

Otitis Media, Acute and Chronic Mastoiditis

CAUSATIVE ORGANISMS: *Staphylococcus aureus*
Streptococcus pyogenes
Pneumococci
Secondary invaders: *Proteus vulgaris*
Bact coli
Ps pyocyanea

Drugs of Choice and Doses

(1) **Penicillin:** (i) (adult dose): 500,000 units, twelve-h intramuscular.

(ii) 200,000 units in 1 c.c. of water instilled post-oper by capillary tube.

(2) **Sulphadiazine** (adult dose): Loading 2 gm., 1·5 gm. hourly for forty-eight hours, 1 gm. four-hourly for th four days; oral.

(3) **Sulphadimidine** (adult dose): Loading 3 to 4 gm., 2 gm. *hourly for forty-eight hours, 1·5 gm. four-hourly for th* four days; oral

Choice of Drug.—Penicillin is the drug of choice for r use. In all cases, however, knowledge of the causative org and its drug sensitivity should be obtained at the start of treat Only by this means can penicillin-insensitive organisms, whi found chiefly in chronic infections, be detected and the c antibiotic prescribed. Thus, aureomycin (for staphylococ *Bact. coli*), streptomycin (for staphylococci, *Bact. coli* or pro chloramphenicol or polymyxin (for *Ps. pyocyanea*) ma necessary.

Special Considerations

(1) **Prompt Treatment.** — Delay in starting treat adversely affects the response to treatment and increases risk of further extension of the infection.

(2) [illegible] to se free dr [illegible] n ha recover [illegible] fness chronic infection.

(3) **Mastoidectomy.**—In the majority of patients it is advis to control spread of infection by antibiotics before underta operation.

The decision to operate is based on accepted surgical princi which have in no way been altered by the advent of chemother Systemic penicillin therapy should be instituted pre-operati and continued until healing takes place, which is usual wi two weeks. Instillation of penicillin at operation and by tube four to five days thereafter hastens recovery and allows prin closure of the wound to be performed with safety.[2]

Criteria of Cure.—Return of temperature to normal, dis pearance of discharge and healing of the drum indicate that in tion is controlled. Local instillation of penicillin will be disc

tinued after four to five days and intramuscular injection after [illegible]

usually be avoided and even myringotomy is less frequently required. On the other hand, in cases coming late under treatment antibiotics are less successful and the need for surgery is more frequent. Chronic otitis media and mastoiditis respond poorly to antibiotics unless they are treated also by adequate surgical measures

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3. GILD, H. S. (1951) Personal Communication.

DRUGS OF CHOICE AND DOSES

(1) **Penicillin:** (i) (adult dose): 500,000 units, twelve-hourly; intramuscular.

(ii) 200,000 units in 1 c.c. of water instilled post-operatively by capillary tube.

(2) **Sulphadiazine** (adult dose): Loading 2 gm., 1·5 gm. four-hourly for forty-eight hours, 1 gm. four-hourly for three to four days; oral.

(3) **Sulphadimidine** (adult dose): Loading 3 to 4 gm., 2 gm. four-hourly for forty-eight hours, 1·5 gm. four-hourly for three or *four days; oral.*

CHOICE OF DRUG.—Penicillin is the drug of choice for routine use. In all cases, however, knowledge of the causative organism and its drug sensitivity should be obtained at the start of treatment. Only by this means can penicillin-insensitive organisms, which are found chiefly in chronic infections, be detected and the correct antibiotic prescribed. Thus, aureomycin (for staphylococci or *Bact. coli*), streptomycin (for staphylococci, *Bact. coli* or proteus), chloramphenicol or polymyxin (for *Ps. pyocyanea*) may be necessary.

SPECIAL CONSIDERATIONS

(1) **Prompt Treatment.** — Delay in starting treatment adversely affects the response to treatment and increases the risk of further extension of the infection.

(2) [illegible] necessary to secure free d[illegible] hastens recove[illegible] fness and chronic infection.

(3) **Mastoidectomy.**—In the majority of patients it is advisable to control spread of infection by antibiotics before undertaking operation.

The decision to operate is based on accepted surgical principles, [illegible] four to five days thereafter hastens recovery and allows primary closure of the wound to be performed with safety.[8]

CRITERIA OF CURE.—Return of temperature to normal, disappearance of discharge and healing of the drum indicate that infection is controlled. Local instillation of penicillin will be discon-

tinued after four to five days and intramuscular injection after

[illegible]

usually be avoided and even myringotomy is less frequently required. On the other hand, in cases coming late under treatment antibiotics are less successful and the need for surgery is more frequent. Chronic otitis media and mastoiditis respond poorly to antibiotics unless they are treated also by adequate surgical measures.

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Chapter XII

INFECTIONS OF THE GASTRO-INTESTINAL TRACT

Bacillary Dysenteries

CAUSATIVE ORGANISMS: *Shigella sonnei*
Shigella flexneri
Shigella shigæ
Shigella schmitzi

DRUGS OF CHOICE AND DOSES

(1) **Sulphadiazine** (adult dose): Loading 2 gm., maintenance 1 gm. four- or eight-hourly; oral.
(See page 16 for details of toxicity.)
(Alternatives: sulphadimidine, sulphathiazole, succinyl sulphathiazole, *or sulphaguanidine.*)
(For details of dosage see page 21.)

(2) **Chloramphenicol** (adult dose): Loading 1·5 gm., maintenance 750 mg. six-hourly; oral.
(For further details see page 46.)

(3) **Streptomycin** (adult dose): 2 gm. eight-hourly; oral.
(For factors determining acquired resistance see page 39.)

CHOICE OF DRUG.—There is little difference between the therapeutic responses to sulphadiazine, chloramphenicol and strepto- [illegible] unless the organism

[illegible]

and sulphathiazole, being more efficacious, are preferred to [illegible]

SPECIAL CONSIDERATIONS

[illegible]

is usually sufficient to correct dehydration and establish free urinary output *in cases of average severity.*

(2) **Anti-dysentery Serum (Shiga).**—Specific anti-dysentery serum (Shiga) has therapeutic value in shiga infections and should be administered intravenously (50,000 to 100,000 units) in all severe cases.

(3) **Symptomatic Treatment.**—Rest and suitable diet materially assist recovery. Rectal irrigations should be used to ease local discomfort.

CRITERIA OF CURE.—In general, specific therapy will be continued for five to seven days, depending on the rate of improvement. [illegible] consecutive negative stool or rectal swab cultures in six weeks, or eight in four weeks, may be accepted as proof of cure.

RESULTS OF TREATMENT.—Clinical and bacteriological cure of shiga and flexner dysentery in favourable cases is achieved in five to seven days, and is more certain when treatment is instituted [illegible] prevent the carrier state.[1]

Bacterial Food Poisoning

CAUSATIVE ORGANISMS *Salmonella typhimurium* (*Salm. aertrycke*)
Salmonella enteritidis (*Salm. gärtner*)
Salmonella paratyphi B
Salmonella cholerae-suis (*B suipestifer*)
etc.

DRUG OF CHOICE

Chloramphenicol (adult dose) Loading 1 5 gm., maintenance 750 mg , convalescent 500 mg six-hourly; oral

(For further details of dosage and toxicity see pages 50 and 47)

SPECIAL CONSIDERATION

Correction of Electrolyte and Fluid Balance.—For severe infections intravenous infusion of saline or Hartmann's solution, in accordance with biochemical needs, is frequently required.

CRITERIA OF CURE.—Maintenance dosage should be given until signs of enteritis and fever have disappeared. Convalescent dosage should be continued for a further five days to prevent bacteriological relapse. Three negative bacteriological examinations of the stools on alternate days may be taken as evidence of final cure.

RESULTS OF TREATMENT.—The results of chloramphenicol therapy in acute bacterial food poisoning are promising, though in a [illegible]
at a [illegible]
carri[illegible]
unsuccessful.

Ulcerative Colitis

SECONDARY INVADERS: Intestinal flora

Improvement of symptoms and of the sigmoidoscopic appearance of the mucosa may follow administration of any of the antibiotics now available. In the uncomplicated disease their therapeutic values are difficult to assess on account of the variable course of the disease, but in the presence of abscesses and fistulæ they may be [illegible]
aureomycin and chloramphenicol, may themselves cause intestinal disturbance.

Infantile Diarrhœa and Vomiting

CAUSATIVE ORGANISMS

The ætiology in individual cases and in unassociated epidemics differs In some the condition is secondary to infection elsewhere in the body (*e.g.*, otitis media, pertussis). In some a virus may be responsible, and in others a specific strain of *Bact. coli.*

CHOICE OF DRUGS.—Antibiotics are of secondary importance in [illegible]
the stools may be successfully achieved by oral administration of streptomycin, chloramphenicol or polymyxin. Even so there is often little or no effect on the course of the dis[illegible]

Chloramphenicol, like aureomycin, [illegible]

disturbance, characterised by vomiting and diarrhœa and replacement of the normal intestinal flora by monilia Thus, the state of the gastro-intestinal tract may not be benefited and may even be affected adversely. More knowledge of the efficacy and side effects of the wide-range antibiotics in this condition is necessary before they can confidently be recommended for routine use. At present they should only be employed with the specific object of eradicating parenteral or intestinal pathogens that are known to be sensitive.

SPECIAL CONSIDERATIONS

(1) Correction of Electrolyte and Fluid Balance.—The basis of early treatment is the correction of dehydration and electrolyte imbalance, by intravenous, or in mild cases intramuscular or subcutaneous, infusions of glucose-saline, plasma, Darrow's or Hartmann's solutions, according to the biochemical need.

(2) Dietetic Management.—Graduation of feeds, in respect of fluids and calories, according to the infant's tolerance is a matter of great importance, and demands close observation, experience and judgment. Errors during the re-establishment of feeding are probably the most common cause of recrudescence and relapse.

RESULTS OF TREATMENT —The mortality of infantile diarrhœa and vomiting in most epidemics is high, ranging from 8 5 to 65 per cent [3] The results of treatment [illegible]

Amœbic Dysentery

CAUSATIVE ORGANISM: *Entamœba histolytica*

DRUGS OF CHOICE AND DOSES

(1) **Emetine hydrochloride** (adult dose): 1 grain daily, subcutaneous injection, for six days
Emetine bismuth iodide (E.B.I.) (adult dose): 3 grains every night for twelve days; oral.
Chiniofon, retention enemata; 200 c.c. of a 2½ per cent. solution, daily.

Carbarsone *(adult dose): 250 mg. twice daily, for twelve* days; oral.

Diodoquin (adult dose): 600 mg three times daily, for twenty days; oral.

(2) **Aureomycin, terramycin** (adult dose): 500 mg six-hourly, oral, for ten days.

(3) **Penicillin** (adult dose): 50,000 units, four-hourly; intramuscular.

(4) **Bacitracin** (adult dose): 20,000 units, six-hourly, oral, for ten days.

CHOICE OF DRUGS.—*Emetine remains the amœbicide of* choice and should form the basis of any régime of treatment, except perhaps in the mild infections of childhood. A combination of penicillin with succinyl sulphathiazole is beneficial by virtue of its ability to control associated bacterial infection, especially in chronic granulomatous lesions. In chronic amœbiasis they should routinely be employed preparatory to emetine therapy. *Aureomycin*[4], *terramycin*[5] *and bacitracin are amœbicidal* (probably by an indirect mechanism) and control dysenteric symptoms, but also allow a disappointing relapse rate. They possess, however, advantages that should justify further trial.

Amœbic hepatitis and other metastatic lesions must be treated with emetine hydrochloride, but in the treatment of intestinal disease emetine bismuth iodide is superior.

SPECIAL CONSIDERATIONS

(1) **Régime of Treatment.**—A course of emetine hydrochloride should be followed directly by a combined course of chiniofon enemata, emetine bismuth iodide and diodoquin. In patients passing cysts only the initial course of emetine hydrochloride may be omitted.[6]

The danger to the heart from emetine overdosage must be continually borne in mind: bed rest for all patients is essential. [illegible] patients [illegible] be considered safe from the risk of relapse or complications. Furthermore, cyst passers are an important reservoir of infection and should receive further courses of treatment. Disappearance of

diazine with streptomycin[7] in the treatment of peritonitis following intestinal perforation; it is at present the preferred antibiotic. Since mixed infections are usual, penicillin, streptomycin and sulphadiazine together are also successful against most combinations of pathogens.[8] The value of combined therapy in comparison with aureomycin has not yet been determined. Intravenous terramycin appears to be highly effective. Bacteriostatic agents applied to the peritoneum, at the time of operation, have little effect on the subsequent course of generalised peritonitis and cannot be considered a therapeutic procedure. They are, however, thought to be of value in preventing spread of early infections still limited to the area of peritoneum adjacent to the primary focus. Whenever possible the bacteriology should be determined from swabs taken at operation, to confirm the suitability of the antibiotics employed.

Special Considerations[9]

Surgery.—Surgery is the fundamental method of treatment, and together with drainage and efficient pre- and post-operative care does more to lower the mortality and improve results than any régime of antibiotic therapy. When peritonitis is established or anticipated, as for instance after operations for obstruction of the large bowel, the administration of antibiotics is indicated and should be commenced at the time of operation. Planned anastomotic operations on the large bowel should be preceded by a full course of phthalyl sulphathiazole to reduce the intestinal flora. It seems probable that the newer antibiotics will be increasingly used because they possess the additional advantage of being effective in pulmonary infections.

Criteria of Cure.—When the cause of peritonitis has been removed and the patient's response is satisfactory, antibiotics may be discontinued forty-eight to seventy-two hours after the temperature has returned to normal. As a rule there is a response within forty-eight hours, and treatment can be discontinued [illegible] post-operative days

iotic therapy

mprovement

is determined largely by the promptness and efficiency of surgical treatment. There can be little doubt, however, that ancillary treatment with antibiotics is beneficial and is responsible for lowering the mortality,[7] especially in spreading non-localised peritonitis and in poor risk patients.

Timely use of antibiotics reduces the incidence of localised infections, such as subphrenic abscess, but is frequently without appreciable benefit when once they are established As a general rule, peritonitis caused by more than one pathogen responds more favourably than peritonitis caused by a single pathogen. The improved prognosis is due not only to more effective control of the peritonitis, but also to prevention of post-operative pulmonary complications.

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Chapter XIII

URINARY TRACT INFECTIONS

CAUSATIVE ORGANISMS: *Bacterium coli*
(*Proteus vulgaris*, *Streptococcus fæcalis*, *Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Bacterium aerogenes*)

Bact. coli Infections

DRUGS OF CHOICE AND DOSES

(1) **Sulphathiazole, Sulphadiazine** (adult dose): Loading 2 gm. first forty-eight hours, 1 gm. four-hourly; maintenance 1 gm *eight-hourly; oral.*
(For details of toxicity see page 16.)

(2) **Chloramphenicol** (adult dose): Loading 2 gm., maintenance 750 mg., six-hourly; oral.
(For further details see page 47.)

(3) **Streptomycin** (in conjunction with sulphonamides) (adult dose). 500 mg. eight-hourly; intramuscular.
(For details of toxicity and acquired resistance see page 37.)

(4) **Polymyxin** (adult dose): 25 mg. four-hourly; intramuscular.

CHOICE OF DRUG.—Sulphonamides are effective in the treatment of *Bact. coli urinary tract infections and remain the most* suitable drugs for routine use. Chloramphenicol and polymyxin, both more potent than sulphonamides, are at the present time employed when the organism is sulphonamide or streptomycin insensitive. Streptomycin is therapeutic in about 60 per cent. of cases, but when used alone has the serious disadvantage of acquired bacterial resistance. Streptomycin is therefore not recommended as the sole antibiotic for routine therapy, but should always be used in conjunction with sulphonamides and alkaline diuretic therapy.

SPECIAL CONSIDERATIONS

Alkalies and Diuresis.—Initial diuresis should be induced by the oral administration of fluids (9 pints daily) and alkalies (potassium citrate 1 to 3 gm. t.d.s. or sodium bicarbonate 1 to 4 gm.

t.d.s.) sufficient to render the urine alkaline. When acute symptoms have abated, usually after three days, fluids may be restricted to 3 pints daily to permit higher concentration of drugs in the urine. Sulphonamide dosage may then be reduced to that required for maintenance.

Since the number of organisms is reduced, and since higher drug concentrations can be reached in the urine, conditions are more favourable to antibacterial action. If streptomycin or chloramphenicol is to be used it should therefore be commenced at this time. The risk of therapeutic failure, particularly with streptomycin, through the appearance of resistant strains is thereby reduced.

[illegible] activity and minimises their side effects. Furthermore, the efficacy of streptomycin is greater in an alkaline urine.

Proteus Infections

DRUGS OF CHOICE AND DOSES

(1) **Streptomycin** (adult dose) 500 mg., eight-hourly; intramuscular.
    (For further details see page 37.)
(2) **Chloramphenicol** (adult dose) Loading 2 gm., maintenance [illegible]

C[illegible] of *Proteus vulgaris* is inconstant and frequently low, its estimation assumes great importance and should, whenever possible, be taken as the guide to treatment and dosage. The majority of strains are most sensitive to streptomycin or chloramphenicol, but a few are found to be within the effective range of penicillin and sulphonamides. Not uncommonly the organism is insensitive to all antibiotics in the highest concentrations obtainable. Whether antibiotics are employed or not, alkaline diuretic therapy forms the basis of treatment.

Bact. aerogenes and *Ps. pyocyanea* Infections

DRUGS OF CHOICE AND DOSES

(1) **Polymyxin** (adult dose): 25-50 mg four-hourly; intramuscular.
    (For further details see page 43.)

(2) **Streptomycin** (adult dose): 500 mg. eight-hourly; intramuscular.
(For further details see page 37.)

(3) **Chloramphenicol** (adult dose): Loading 2 gm., maintenance 750 mg. six-hourly; oral.
(For further details see page 47.)

CHOICE OF DRUG.—The superior potency of polymyxin against [illegible]

phenicol may be preferred, or aureomycin, if enterococci predominate. It would seem best, however, to include polymyxin in any scheme of treatment.

Strep. fæcalis (Enterococcal) Infections

DRUGS OF CHOICE

(1) **Streptomycin with penicillin.**
Streptomycin (adult dose): 500 mg. eight-hourly; intramuscular.
(For further details see page 37.)
Penicillin (adult dose): 300,000 units eight-hourly; intramuscular.
(For further details see page 29.)

(2) **Aureomycin** (adult dose): Loading 750 mg., maintenance [illegible]

C[illegible] difference between the therapeutic efficiencies of aureomycin alone and penicillin with streptomycin, either treatment may be used. In all cases, full use [illegible]

mum benefit from the latter drug.

Staphylococcus aureus Infections

DRUGS OF CHOICE

(1) **Penicillin** (adult dose): 300,000 units eight-hourly; intramuscular.
(For further details see page 32.)

) **Aureomycin** (adult dose): Loading 750 mg, maintenance 500 mg. six-hourly; oral.

(For further details see page 57.)

) **Sulphadiazine** (adult dose): Loading 2 gm., first forty-eight hours 1 gm. four-hourly; maintenance 0 5 gm. six-hourly; oral. (Alternative, sulphadimidine.)

(For details of toxicity, etc., see page 16.)

) **Chloramphenicol** (adult dose): Loading 2 gm., maintenance 750 mg. six-hourly; oral.

(For further details see page 47.)

) **Streptomycin** (adult dose): 500 mg. eight-hourly; intramuscular.

(For further details see page 37.)

CHOICE OF DRUG—Penicillin is the most effective antibiotic, [illegible]

[illegible]

PECIAL CONSIDERATIONS

(1) **The Influence of Underlying Lesions.**—Benefit from ntibiotics will be no more than temporarily successful if predisosing pathological conditions remain uncorrected In patients affering from recurrent acute pyelitis or chronic pyelitis, investiation of the urinary tract should be made to detect such lesions—g., obstruction, calculus or tuberculosis.

(2) **The Influence of Renal Function.**—Impairment of renal unction, which implies a proportionate reduction in ability to oncentrate drugs and other excreted substances, may be sufficiently evere to prevent therapeutic concentrations of drugs being reached n the urine. Simultaneously, their retention causes abnormally igh serum concentrations, which may be dangerous if the drug is otentially toxic.

When renal function is [illegible] n the u [illegible] llows a [illegible] ffective against sensitive organisms. Standard doses, as used for ystemic infections, may thus be effective against organisms insensiive to the highest levels obtainable in the blood (e g, some strains of *Strep.* [illegible]

biotic, but upon the amount present in the active form. As has been described elsewhere, this varies with different antibiotics, being relatively small with chloramphenicol, intermediate with sulphonamides and large with terramycin and penicillin.

Gross impairment of renal function may also prevent adjustment of urinary *pH*, by administration of alkalies or acids, and prevent diuresis when fluids are given. Thus the success or failure of even the best treatment of urinary infection depends primarily on the functional efficiency of the kidneys.

(3) **Infections of Deep Tissues.**—Antibiotics in the urine are effective only against organisms lying free in the urine or superficially in the epithelium. Owing to lack of permeation they are ineffective against organisms buried in the walls of the urinary passages. Thus the urine can be kept sterile as long as it contains adequate concentrations of antibiotic, even though there may be continuing leakage of bacteria from active foci in inaccessible situations. It follows that while antibiotics are being administered a sterile urine is not proof that infection has been eradicated.

Effective local concentrations at the site of deep infections, such as pyelonephritis or prostatitis, are dependent on the level in the blood, for which the dosage must be the same as that for tissue infections elsewhere.

(4) **Mixed Infections.**—In chronic infections a mixed bacterial flora, whose constituent organisms differ in their susceptibilities to antibiotics, is commonly found. It is imperative to know the types of organisms and their sensitivities, so that the antibiotic or *combination of antibiotics possessing the necessary range of action may be used.*

Criteria of Cure.—Specific treatment should be continued for a week, or if the response, as judged by the fall of temperature and [illegible] Bacteria- [illegible]

[illegible] or an underlying lesion is suspected, examination should be repeated at fortnightly intervals for two months or more. As has already been [illegible] so long as any predis- [illegible] tions [illegible] and mixed infections show a higher proportion of failures and relapses. Renal failure, uncorrected predisposing conditions, and the presence in the urine of organisms insusceptible to available antibiotics increase the probability of failure.

Abacterial Pyuria

CAUSATIVE ORGANISM: Undetermined.

DRUGS OF CHOICE AND DOSES

(1) **Novarsenobillon** or **Neoarsphenamine** (adult dose) 0·3 gm.; three intravenous injections at weekly intervals.[1]

(2) **Aureomycin** (adult dose). Loading 750 mg., maintenance 500 mg. six-hourly; oral, for five to seven days.

CHOICE OF DRUG.—Neoarsphenamine has proved highly effective, but early experiences with aureomycin are encouraging and indicate that it may find a place in treatment.

SPECIAL CONSIDERATIONS

Differential Diagnosis.—It is imperative that other organic and infective conditions which may simulate abacterial pyuria are excluded by appropriate investigations.

CRITERIA OF CURE.—It is recommended that patients should be kept under surveillance for three months, after relief of symptoms and disappearance of discharge.[2]

RESULTS OF TREATMENT.—Three injections of N.A.B. are curative in virtually all cases in three to six weeks. Aureomycin is reported to give symptomatic relief and eradicate pyuria with greater rapidity.[3]

Antibiotics in Urogenital Surgery

In urogenital surgery, as in general surgery, technical perfection is more important than antibiotic therapy in the prevention of infection. When there is special need for prophylaxis by antibiotics, as in patients with heart lesions or chest infections, penicillin is most widely used. Aureomycin and probably terramycin may prove superior, as they are effective against the flora of the respiratory tract, in addition to that of infections of the urinary tract.

Whenever circumstances allow, existing infection should be brought under control by antibiotic therapy before surgery is undertaken. If this is impracticable, penicillin or whichever antibiotic is indicated by the bacteriology should be commenced at operation and continued for at least four days thereafter.

Exacerbation of infection, as a result of procedures such as instrumentation, may be avoided by prior administration of a suitable antibiotic, which should be continued post-operatively for at least four days.

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Chapter XIV

INFECTIONS OF THE BRAIN AND MENINGES

Purulent Meningitis

CAUSATIVE ORGANISMS: Meningococci (*Neisseria meningitidis*)
Hæmophilus influenzæ
Pneumococci
(*Bact. coli*, *Ps. pyocyanea*, *Staph. aureus*, *Str. pyogenes*)

In every case, effective treatment must be started as soon as cerebrospinal fluid has been withdrawn for diagnostic purposes and must not be delayed until the bacteriological diagnosis is confirmed. When the ætiology is uncertain, on clinical grounds, initial therapy must be of sufficiently wide range to cover all of [illegible] Sulphadiazine or sulphadimidine with [illegible] ...ate therapy, as recom... [illegible] ...d when treatment is [illegible]

Meningococcal Meningitis

DRUGS OF CHOICE AND DOSES

(1) [illegible] (adult dose): Loading 3 gm. intramuscular; [illegible] gm.

(For further details see page [illegible])

(2) **Penicillin** (adult dose): 250,000 units four-hourly intramuscular, and 25,000 units daily intrathecal.

(For further details see page 34.)

(3) **Aureomycin** *(adult dose)*: Loading 1 gm. intravenous, 1·5 gm. oral; maintenance 750 mg. six-hourly, oral.

(For further details see page 57.)

CHOICE OF DRUG.—Sulphadiazine, sulphadimidine and "Sulphatriad" *are the most rapidly curative agents.* Systemic penicillin,

units or more four-hourly) to reach the cerebrospinal fluid in therapeutic amounts. Aureomycin should be reserved for the treatment of infections resistant to sulphonamides and penicillin.

SPECIAL CONSIDERATIONS

Bacteriological Diagnosis.—Examination of the cerebrospinal fluid provides the only reliable confirmation of diagnosis and is essential for determining the sensitivity of the organism, which may show considerable initial variation.

CRITERIA OF CURE.—Improvement in mental state takes place within twenty-four hours in favourable cases. The temperature usually falls in two to four days and is followed by disappearance of *neck stiffness and headache. Treatment should be continued* until the temperature has remained normal for four days and no signs of meningeal irritation persist. Absence of improvement within forty-eight hours or recurrence of fever call for immediate *review of treatment and dosage, with reference to the sensitivity* of the organism and the drug concentration in the spinal fluid. There should be no hesitation in giving penicillin by the intrathecal and intramuscular routes.

RESULTS OF TREATMENT.—The overall mortality has been reduced from over 60 per cent. to about 1 per cent. by sulphonamides. The fatality rate remains highest in infancy, in pregnancy and in late life, in those in whom there is delay in starting effective therapy, and in fulminating infections.

Hæmophilus influenzæ Meningitis

DRUGS OF CHOICE AND DOSES

(1)

ars): 20 mg. per
vith 50 to 75 mg
(according to bacterial sensitivity) in 2 c.c. pyrogen-free distilled water, daily, *intrathecal.*

(For further details see page 39.)

Sulphadiazine (doses for children under 3): Loading 0·75 gm. intramuscular; first forty-eight hours 0·5 gm. four-hourly, intramuscular or oral; maintenance 0·25 to 0·5 gm. six-hourly, oral.

(For further details see page 16.)

(2) **Aureomycin** (doses for children under 3): Loading 300 mg., maintenance 150 mg. four-hourly; oral.

(For further details see page 57.)

(3) **Chloramphenicol** (doses for children under 3). Loading 750 mg., maintenance 500 mg. six-hourly, oral.

(For further details see page 50.)

(4) **Polymyxin** (doses for children under 3): (*a*) 0·5 mg. per pound of body weight, four-hourly, intramuscular. (*b*) 2 to 3 mg. in 2 c.c. pyrogen-free distilled water, once or twice daily, intrathecal.

(For further details see page 45.)

CHOICE OF DRUGS.—Streptomycin with sulphadiazine is the most widely used and effective remedy. The newer antibiotics show promise of great therapeutic value, though at present the number of patients treated is too small to allow a final assessment to be made.[2,3,4] Many strains of *H. influenzæ, type B*, are partially sensitive to penicillin *in vitro*, but human infections due to these strains respond poorly.

Type-specific rabbit antibody has been recommended for the treatment of severe infections, but, with an adequate antibiotic régime, is of doubtful additional value and is rarely employed in this country.

SPECIAL CONSIDERATIONS

(1) **Bacteriological Diagnosis.**—When a diagnostic lumbar puncture has been performed, treatment must be initiated without delay. Intrathecal dosage must be sufficient to give concentrations which exceed those found to be inhibitory *in vitro*, and thus may be higher than that recommended.

(2) **Convulsions.**—Routine administration of phenobarbitone (¼ to ½ grain three times daily) is imperative for the prophylaxis of convulsions.[5,6]

CRITERIA OF CURE.—The cerebrospinal fluid usually becomes sterile in about forty-eight to seventy-two hours. The temperature starts to fall and clinical improvement becomes apparent at the end of this time; irritability and neck stiffness usually persist somewhat longer.

mycin or polymyxin should be given twice daily at the start of treatment until there are signs of improvement.

Ps. pyocyanea meningitis

Treatment in the past has been most unsuccessful, but polymyxin, which is the most active antibiotic against *Ps. pyocyanea*, has been found to exert a therapeutic effect in the human disease and should therefore be employed.[11]

Administration by the intrathecal and intramuscular routes, as described for the treatment of meningitis due to *H. influenzæ*, is necessary.

Brain Abscess and Extradural Abscess

CAUSATIVE ORGANISMS: *Staphylococcus aureus*
Pneumococci
(Secondary invaders, such as *Ps. pyocyanea*)

DRUG OF CHOICE AND DOSES

Penicillin (adult dose): 500,000 to 1,000,000 units twice daily, intramuscular, for at least two weeks, with local instillation of 1,000 units per c c. of water.

SPECIAL CONSIDERATIONS[12]

Surgery.—In early cases aspiration of pus through a small burr hole and instillation of penicillin is the recommended procedure for obtaining adequate local concentrations and for the [illegible]

[illegible]

operatively for seven days by the systemic route, and, if meningitis is present, by the intrathecal route also. Pus from each aspiration must be examined bacteriologically, as mixed infections often containing penicillin-resistant organisms, such as *Ps. pyocyanea*, are not uncommon.

RESULTS OF TREATMENT.—The mortality of brain abscess, irrespective of site or ætiology, is about 50 per cent. It is thought that antibiotics in conjunction with surgery will bring about further reduction. In those who survive there remain many with permanent sequelæ, such as epilepsy.[11]

Cavernous Sinus Thrombosis, Lateral Sinus Thrombosis

CAUSATIVE ORGANISMS: *Staphylococcus aureus*
Pneumococci

DRUG OF CHOICE AND DOSE

Penicillin (adult dose): Loading dose 200,000 units, maintenance 100,000 units four-hourly; intramuscular.
(For further details see page 34.)

CHOICE OF DRUG.—Aureomycin may be employed as an alternative to penicillin if the infection is due to staphylococci, which are highly resistant to penicillin.

SPECIAL CONSIDERATIONS

(1) **Meningitis.**—Coexistent meningitis requires immediate intrathecal therapy as described on page 108.

[illegible]

(3) **Primary Lesion.**—When mastoiditis is the cause of thrombosis of the lateral sinus, surgical treatment, as described on page 88, in addition to penicillin therapy, may be necessary

CRITERIA OF CURE.—In early cases which respond rapidly, antibiotics may be stopped after seven days. Often, however, treatment for two to three weeks is required.

RESULTS OF TREATMENT.—Sinus thrombosis carried a high mortality before penicillin was available. Now approximately 70 per cent. make a permanent recovery, though in some patients there are sequelæ, such as loss or impairment of vision.

Neurosyphilis (including Meningo-vascular Syphilis, Tabes Dorsalis and General Paresis)

CAUSATIVE ORGANISM *Treponema pallidum*

DRUGS OF CHOICE

(1) **Procaine Penicillin G** (adult dose). 600,000 units daily, intramuscular, for twelve to twenty days,[13] two or more courses at three-monthly intervals
(2) **Bismuth Oxychloride:** 0·2 gm. weekly, intramuscular, for six weeks.

(3) **Malarial Therapy:** Eight to ten rises of temperature to 104°F.

CHOICE OF DRUGS.—Penicillin is the most potent spirochætocidal agent available and is the basic drug in treatment. In order to *minimise the risk of precipitating reactions*, a preliminary course of bismuth should be given.[16,17] Such a delay in starting penicillin may be unjustifiable if the disease is of recent onset. There is divergence of opinions regarding the necessity for arsenotherapy, but it is now generally considered to be unnecessary. In the treatment of general paralysis of the insane, taboparesis, spastic paraplegia, etc., malarial therapy should also be used, unless *contraindicated*[15] *by other considerations. Aureomycin and to a* lesser extent chloramphenicol are active against spirochætes, but do not appear to be as effective as penicillin[16] and have no place in routine treatment.

SPECIAL CONSIDERATIONS

Limitations of Penicillin Therapy.—Penicillin may be expected to bring about improvement of symptoms and physical signs caused by inflammatory processes, but not of those due to degenerative changes.

CRITERIA OF CURE.—Normal cell and protein content and negative Wassermann reaction of the cerebrospinal fluid, persisting after treatment, is considered to indicate that infection is controlled. Six months or longer may elapse before the serological reaction becomes negative. If the titre is not falling in four months [illegible] be given on the assumption

[illegible] *pes of neurosyphilis rapid* improvement in the cytology and protein content of the cerebrospinal fluid takes place. The serological reaction is converted and remains negative in 90 per cent. of patients for three years, while in about 10 per cent. of the patients treated, abnormalities of the fluid return after this time.[17] The results of penicillin in conjunction with malarial therapy in general paralysis of the insane are [illegible]

[illegible]

in gummatous and meningitic cases more complete recovery is possible.

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Chapter XV

MISCELLANEOUS INFECTIONS

Cellulitis (including Infections of the Hand)

CAUSATIVE ORGANISMS: *Staphylococcus aureus*
Streptococcus pyogenes

DRUGS OF CHOICE AND DOSES

Penicillin (adult dose): Loading, 200,000 units crystalline penicillin with 600,000 units procaine penicillin; maintenance 3-600,000 units procaine penicillin daily or 200,000 units crystalline penicillin twice daily; intramuscular.

(For further details see page 34.)

Aureomycin (adult dose): Loading 750 mg., maintenance 500 mg. *six-hourly; oral.*

(For further details see page 57.)

Sulphadiazine (adult dose): Loading 2 gm. first forty-eight hours, 1 gm. four-hourly; maintenance 1 gm. eight-hourly; oral.

(Alternatives: sulphadimidine or sulphamerazine.)

(For further details see page 21.)

CHOICE OF DRUGS.—Penicillin is the most effective agent and is recommended for the treatment of all infections, except those due to penicillin-resistant staphylococci, for which aureomycin is preferred. Sulphonamides should only be used in mild infections where there is no risk of extension to important structures, such as bones or tendon sheaths, and never for infections of the hand.

SPECIAL CONSIDERATIONS

Surgery.—While prompt chemotherapy alone cures many infections, surgical drainage must be undertaken when the accepted indications are present.

CRITERIA OF CURE.—When the temperature has returned to normal and local signs of active inflammation have disappeared, penicillin may be stopped. In severe infections or in those which have responded slowly antibiotics should be continued for a

further three to four days It is not uncommon for the clinical response to be delayed until the third to fourth day of treatment.

RESULTS OF TREATMENT.—When treatment is instituted before tissue necrosis has become gross, complete resolution without recourse to surgery is the rule. When abscesses are present, and if free drainage is not established, recovery is delayed and complications are more frequent.

Osteomyelitis

CAUSATIVE ORGANISMS *Staphylococcus aureus* (*Streptococcus pyogenes*)

DRUGS OF CHOICE AND DOSES

(1) **Penicillin** (adult dose): (*a*) Loading, at least 400,000 units; maintenance 250,000 twice daily, intramuscular, for two to four weeks

(*b*) Local instillation 25,000 units per c.c. once or twice daily

(For further details see page 34.)

(2) ***Aureomycin*** *(adult dose): Loading 1 gm, maintenance* 750 mg. six-hourly; oral

(For further details see page 57.)

CHOICE OF DRUGS.—Penicillin being most effective is the preferred antibiotic. When the organism is partially insensitive, higher dosage must be used to give concentrations greater than those shown to be inhibitory in the laboratory. If the organism is completely insensitive to penicillin aureomycin should be used Every effort must therefore be made to isolate the organism from aspirated pus or blood culture, so that its drug sensitivity may be estimated.

SPECIAL CONSIDERATIONS

(1) **Drainage.**—Tension within the bone must be reduced to prevent the sequestration which follows thrombosis. Soft tissue abscesses require aspiration or incision As a rule repeated aspiration once or twice daily is sufficient for this purpose (penicillin instillations being performed at the same time). Pus must be regularly examined bacteriologically, since secondary invaders, resistant to penicillin but sensitive to other antibiotics, may gain access.

Open surgery for the removal of detached sequestra should . delayed until infection has subsided [1]

(2) **Immobilisation.**—Immobilisation of the affected part *must be carried out in accordance with the general principles of* treatment of inflammation.

CRITERIA OF CURE.—As small inaccessible foci of bacteria may linger in the bone for two or three weeks, without there being

present treatment may be required for as long as six weeks.

RESULTS OF TREATMENT.—Early institution of treatment before compression has caused thrombosis, and the avoidance of secondary

months. In about 80 per cent. of cases complete cure may be expected.[1]

In chronic osteomyelitis active infection may be arrested in 70 per cent. of cases. Adequate surgical measures must be employed, in conjunction with penicillin (or the appropriate antibiotic) *therapy, to prevent relapse and obtain satisfactory healing.*

Septic Arthritis

The causative organisms and principles of treatment are the same as those of osteomyelitis. Penicillin 50,000 units should be injected into the affected joint daily for two to three weeks and adequate drainage must be ensured.

Tetanus

CAUSATIVE ORGANISM: *Clostridium tetani*

DRUGS OF CHOICE AND DOSES

(1) **Antitoxic Serum:** (*a*) Prophylactic: 1,500-3,000 units; intramuscular. (*b*) Therapeutic: 200,000-800,000 units; intravenous.

(2) **Penicillin** (adult dose): 300,000 units twice daily; intramuscular.

(For further details see page 34.)

SPECIAL CONSIDERATIONS

Injection of antitoxic serum forms the basis of prophylaxis and treatment, though it is effective only in neutralising circulating toxin and not that already fixed in the nervous system. Penicillin is not curative, since its action is solely on the organism. The aim of giving penicillin is, by sterilising the wound, to prevent further toxin production. The intravenous is the preferred route for administration of antitoxin, since it is probably superior and certainly safer than the intrathecal route

(1) **Control of Spasms.**—The relief of spasms is of great importance, and may be achieved by a drug such as bromethol (0 1 mg. per kilogram of body weight) administered eight-hourly *per rectum*.

(2) **Management.**—Though often a matter of difficulty, it is imperative to ensure a sufficient intake of calories (2,000 C. daily) and fluids. If the patient is unable to take nourishment by mouth, alternative routes (nasal catheter or intravenous infusion) must be used.

RESULTS OF TREATMENT —The value of penicillin has not been clearly defined, owing to the absence of sufficient numbers of cases. It is unlikely, however, that the prognosis is greatly improved in comparison with that resulting from adequate antitoxic therapy combined with measures to control spasm.

Gas Gangrene

CAUSATIVE ORGANISMS. *Clostridium welchii*
Clostridium sporogenes
Clostridium septicum
Clostridium œdematiens

DRUGS OF CHOICE AND DOSES

Penicillin with Sulphadiazine and Antitoxin.

Penicillin (adult dose). Loading 200,000 units, maintenance 100,000 units four-hourly; intramuscular.

(For further details see page 34)

Gas gangrene antitoxic sera: (*a*) Therapeutic: 10,000-20,000 units (*Cl. welchii, Cl. septicum*); 50,000-100,000 units (*Cl. œdematiens*); intravenous and local injection (*b*) Prophylactic: 5,000 units (*Cl. welchii, Cl. septicum*); 20,000 units (*Cl. œdematiens*); intramuscular.

Sulphadiazine (adult dose): Loading 3 to 4 gm., first forty-

(2) **Immobilisation.**—Immobilisation of the affected part must be carried out in accordance with the general principles of treatment of inflammation.

CRITERIA OF CURE.—As small inaccessible foci of bacteria may linger in the bone for two or three weeks, without there being

shorter course may suffice, but for those in whom sequestration is present treatment may be required for as long as six weeks.

RESULTS OF TREATMENT.—Early institution of treatment before compression has caused thrombosis, and the avoidance of secondary infection by penicillin-resistant organisms, are the most important factors in prognosis. Even if bone destruction is extensive, provided that only small sequestra are present at the end of treatment, complete resolution may still occur after a period of weeks or months. In about 80 per cent. of cases complete cure may be expected.[1]

In chronic osteomyelitis active infection may be arrested in 70 per cent. of cases. Adequate surgical measures must be employed, in conjunction with penicillin (or the appropriate antibiotic) therapy, to prevent relapse and obtain satisfactory healing.

Septic Arthritis

The causative organisms and principles of treatment are the same as those of osteomyelitis Penicillin 50,000 units should be injected into the affected joint daily for two to three weeks and adequate drainage must be ensured.

Tetanus

CAUSATIVE ORGANISM: *Clostridium tetani*

DRUGS OF CHOICE AND DOSES

(1) **Antitoxic Serum:** *(a) Prophylactic: 1,500-3,000 units;* intramuscular. (*b*) Therapeutic: 200,000-800,000 units; intravenous.

(2) **Penicillin** (adult dose): 300,000 units twice daily; intramuscular.

(For further details see page 34.)

SPECIAL CONSIDERATIONS

Injection of antitoxic serum forms the basis of prophylaxis and treatment, though it is effective only in neutralising circulating toxin and not that already fixed in the nervous system. Penicillin

administration of antitoxin, since it is probably superior and certainly safer than the intrathecal route

(1) **Control of Spasms.**—The relief of spasms is of great importance, and may be achieved by a drug such as bromethol (0 1 mg per kilogram of body weight) administered eight-hourly *per rectum*

must be used

RESULTS OF TREATMENT.—The value of penicillin has not been clearly defined, owing to the absence of sufficient numbers of cases. It is unlikely, however, that the prognosis is greatly improved in comparison with that resulting from adequate antitoxic therapy combined with measures to control spasm.

Gas Gangrene

CAUSATIVE ORGANISMS *Clostridium welchii*
Clostridium sporogenes
Clostridium septicum
Clostridium œdematiens

DRUGS OF CHOICE AND DOSES

Penicillin with Sulphadiazine and Antitoxin.

Penicillin (adult dose): Loading 200,000 units, maintenance 100,000 units four-hourly, intramuscular.

(For further details see page 34.)

Gas gangrene antitoxic sera: (*a*) Therapeutic· 10,000-20,000 units (*Cl. welchii*, *Cl. septicum*); 50,000-100,000 units (*Cl. œdematiens*); intravenous and local injection. (*b*) Prophylactic: 5,000 units (*Cl. welchii*, *Cl. septicum*), 20,000 units (*Cl. œdematiens*); intramuscular

Sulphadiazine (adult dose): Loading 3 to 4 gm., first forty-

eight hours 1·5 gm. four-hourly, maintenance 1 gm. fo
hourly; oral.

(Alternatives: sulphadimidine, sulphamerazine.)

(For further details see page 21.)

CHOICE OF DRUGS.—Penicillin and sulphonamides should administered, in conjunction with early and efficient surgery all cases and with antitoxin in severe cases. Although sulphadiazi is less effective than penicillin, the combination is recommend in order to achieve the maximal therapeutic benefit. Aureomy is also active against clostridia *in vitro*, but its value in the tre ment of human infections has not been assessed.

CRITERIA OF CURE.—When infected tissues have been co pletely excised, penicillin and sulphonamides may be stopped af four days. If complete excision is not possible, chemothera should be continued for five to ten days.[2]

RESULTS OF TREATMENT.—Antibiotics and antitoxin, when us early and in conjunction with surgery, have brought about co siderable improvement in the recovery rate. During the seco World War, the mortality rate fell from over 50 per cent. in 19 to about 20 per cent. in 1944 and 1945.[3] Efficient prophylaxis a surgical treatment still remain of paramount importance and wi antibiotics have done most to improve the prognosis.

Actinomycosis

CAUSATIVE ORGANISMS: *Actinomyces bovis*
Actinomyces israeli
Actinomyces asteroides

DRUGS OF CHOICE AND DOSES

(1) **Penicillin with Sulphadiazine**
Penicillin (adult dose): 500,000 units three times daily, intr

n

four-hourly; oral.

(Alternatives: sulphamerazine, sulphadimidine.)

(For further details see page 21.)

(2) **Streptomycin with Sulphadiazine**
Streptomycin (adult dose): 1 to 2 gm. daily for at least on month; intramuscular.

(For further details see page 41.)

diazine are recommended.[4] Aureomycin has been shown to be rapidly therapeutic in mandibular actinomycosis,[5] but is still largely untried in actinomycosis in other situations

SPECIAL CONSIDERATIONS

(1) **Surgery.**—Surgical intervention may be required for excision of gross visceral lesions or to secure drainage of abscesses too large to be treated by aspiration.[4]

(2) **General Management.**—General measures for the maintenance of nutrition and for combating anæmia are necessary adjuncts to treatment. X-rays and tincture of iodine (5 minims *t d.s in milk*) *still have a place in treatment.*

CRITERIA OF CURE.—Sulphonamides should be stopped after ten days, but penicillin or streptomycin must be continued for some weeks after clinical signs have subsided Further courses of treatment, which may be repeated over a year if necessary, will be given if there [illegible] or persistence of the infection

being seen in actinomycosis of the face and of bone.[3]

Anthrax

CAUSATIVE ORGANISM. *Bacillus anthracis*

DRUGS OF CHOICE AND DOSES

Penicillin (adult dose): 100,000 units four-hourly; intramuscular. (For further details see page 34)

Sclavo's Serum: 100 to 200 c c., intravenous, repeated after twenty-four hours if there is no improvement

CHOICE OF DRUGS —Penicillin is the more potent drug and, given alone, rapidly eradicates the organism and brings about cure in patients with malignant pustule. Local œdema may increase for twenty-four to forty-eight hours after starting therapy in spite of general improvement. In cases of pulmonary and visceral anthrax *it is advisable to give serum in addition. Aureomycin,*

chloramphenicol and streptomycin are active against *B. anthracis*, but have not been extensively tried in the human infection.

CRITERIA OF CURE.—Malignant pustule, in favourable cases, subsides and commences to heal in four to five days; treatment for seven days is usually sufficient. In severe or bacteræmic cases the response is slower, and treatment may be required for fourteen days.

RESULTS OF TREATMENT.—Sclavo's anti-anthrax serum brought about a considerable reduction in the mortality of malignant pustule. Penicillin has still further improved the prognosis, increased the rate of healing and reduced the need for surgical excision in this type of lesion Experience of penicillin in the treatment of visceral lesions is too limited to allow an assessment to be made.

BIBLIOGRAPHY

Chapter XVI

SEPTICÆMIAS

Typhoid and Paratyphoid Fevers

CAUSATIVE ORGANISMS: *Salmonella typhi*
Salmonella paratyphi B
Salmonella paratyphi A

DRUG OF CHOICE AND DOSE

Chloramphenicol (adult dose)· Loading 4 gm.; maintenance 0 5 gm. four-hourly until apyrexial, then 500 mg. six-hourly for seven days, followed by 500 mg. twice daily for seven days, oral.

(For further details of dosage see page 50.)[1,2,3]

SPECIAL CONSIDERATIONS

[illegible]

temporary deterioration of the patient's condition (see page 48)

(3) Initial Therapy in the Semi-conscious Patient.—[illegible]

the recommended loading dose.

CRITERIA OF CURE.—The average duration of fever after the start of treatment is about three to five days[3] and clinical improvement takes place with equal rapidity in favourable cases Blood cultures usually become sterile within four days, urine cultures within two days and stool cultures at some time during treatment, though they may later become positive.[4] Relapses respond to chloramphenicol as satisfactorily as primary infections and delay in starting treatment does not appear to interfere with the thera-

peutic response.[3] As intestinal hæmorrhage and perforation may occur during treatment after the patient has become apyrexial,[3] no relaxation of medical care is permissible until convalescence is well established. Relapse may occur between six and thirty-one days after the temperature has returned to normal

Results of Treatment.—The mortality rate of typhoid fever has been reduced to 6·5 per cent.[3] and the incidence of serious complications has shown similar improvement. Thus, although chloramphenicol often has a dramatic effect on the course of the disease, it does not save every patient. Relapse rates as high as 27·5 per cent have been encountered with courses of less than fourteen days' duration.[3]

Typhoid Carriers and Convalescent Excreters

Chloramphenicol may bring about sterility of the stools and urine so long as administration is continued, but upon withdrawal relapse frequently takes place.

Weil's Disease (Leptospirosis)

Causative Organisms. *Leptospira icterohæmorrhagiæ*
Leptospira canicola

Drugs of Choice and Doses

Penicillin (adult dose): Loading 200,000 units, maintenance 100,000 units four-hourly; intramuscular.

Choice of Drug.—Penicillin is the antibiotic of first choice in the treatment of Weil's disease. Experimentally, aureomycin has been shown to be active, and successful reports of its use in the human disease have been made.[5] At the present time its thera-
[illegible] shown to be superior to that of penicillin.
[illegible]
affects the course of the disease unless instituted during the first week.

Undulant Fever (Brucellosis)

Causative Organisms: *Brucella abortus*
Brucella melitensis
Brucella suis

DRUGS OF CHOICE AND DOSES

Aureomycin with Streptomycin:[7]

[illegible]

C [illegible]

potent, weight for weight, than streptomycin or chloramphenicol.[9] Streptomycin, however, enhances the effect of the newer antibiotics[6] and is thought to reduce the liability to relapse. When streptomycin is so employed there appears to be little risk of the emergence of streptomycin-resistant strains. Up to 4 gm. of

[illegible] treat-
[illegible] utinely
[illegible] ion of

treatment, and the question of subsequent suppressive therapy to prevent relapses, are at present not decided

SPECIAL CONSIDERATION

Herxheimer-like Reactions.—A mild and usually transient increase of fever and toxæmia has been reported during the first few hours of [illegible]

[illegible]

treatment for a longer period—*i e.*, at least twenty-eight days—is advisable. Patients should be kept under observation for several months before permanent cure can be assumed

RESULTS OF TREATMENT.—By employing concurrent aureomycin and dihydrostreptomycin, the cure rate has been raised and the incidence of relapses reduced to figures ranging between 22 and 5 per cent.[7,10] Chronic brucellosis and local complications may respond favourably, but too often results are disappointing. The

variable course of the untreated disease makes it difficult to assess the beneficial effect of antibiotics in individual patients.

Tularæmia

CAUSATIVE ORGANISM: *Brucella tularensis*

DRUG OF CHOICE AND DOSE

Streptomycin (adult dose): 250 mg. six-hourly, intramuscular, for at least six days.

(For further details see page 41.)

CHOICE OF DRUG.—At the present time streptomycin is recommended for the treatment of tularæmia. Aureomycin has been

rapidity. Fever subsides and constitutional symptoms improve, as a rule within two days. The clinical and radiological abnormalities improve more slowly.

Plague

CAUSATIVE ORGANISM: *Pasteurella pestis*

DRUGS OF CHOICE AND DOSES

Streptomycin with Sulphadiazine:[19]

Streptomycin: 1 gm. six-hourly, intramuscular, until third

for five days.)

(Alternative, sulphamerazine.)

(For further details see page 21.)

ce in plague.

but should

for the pre-

ramphenicol

and terramycin being active against the experimental disease, should be tried if there is no response to streptomycin within three days. One of these antibiotics together with antiplague immune serum globulin (rabbit) are recommended in addition to streptomycin in severe septicæmic and pneumonic infections

RESULTS OF TREATMENT.—Sulphonamides and antiserum have reduced the mortality to about 30 per cent, streptomycin therapy has further lowered it to 15 per cent. or less [13]

Rickettsial Infections

CAUSATIVE ORGANISMS

Scrub typhus	due to	*Rickettsia*	*nipponica* (*R. orientalis*)
Epidemic typhus	,,	,,	*prowazeki*
Brill's disease	,,	,,	*prowazeki*
Murine typhus	,,	,,	*mooseri*
Rocky Mountain spotted fever	,,	,,	*rickettsi*
Tickbite fever	,,	,,	*rickettsi* var *pijperi*
Rickettsial pox	,,	,,	*akari*
Q fever	,,	,,	*burneti*

CHOICE OF DRUG.—Chloramphenicol, aureomycin and terramycin possess marked anti-rickettsial activity. Weight for weight, terramycin is the most active, but in the treatment of human disease may be less consistent,[14] and at the present time its comparative status has not been fully defined. The efficacy of aureomycin and chloramphenicol is of the same order, although one or the other may be slightly superior in individual infections.

DOSAGE

Chloramphenicol (adult dose): Loading 3 to 4 gm, maintenance 1 gm six-hourly; oral

(For further details see page 50.)

Aureomycin (adult dose): Loading 1 gm, 750 mg six-hourly; oral

(For further details see page 57.)

Scrub Typhus

Four to five grams of chloramphenicol given over a period of twenty-four hours has been shown to be uniformly satisfactory.[15,16] Toxæmia disappears within twenty-four hours and the tempera-

ture returns to normal in forty-eight hours. The mortality, which previously was 10 per cent., and the need for prolonged convalescence, are now negligible.

Epidemic Typhus

Aureomycin is preferred for the treatment of epidemic typhus and of the recrudescent form, known as Brill's disease. Treatment should be continued until the patient has been apyrexial for at least forty-eight hours. The extent of reduction of the mortality rate, while impressive, has at the present time not been fully assessed. In Brill's disease the temperature falls in one or two days; the mortality, even in untreated patients, is very low.[17]

Murine Typhus

Murine typhus responds rapidly to both aureomycin and chloramphenicol,[18] the temperature returning to normal within three days.

Rocky Mountain Spotted Fever

Both aureomycin and chloramphenicol are rapidly effective in the treatment of Rocky Mountain spotted fever, and there appears to be little difference in their value. Both antibiotics are greatly superior to para-aminobenzoic acid. The duration of fever is reduced to twenty-four or forty-eight hours, compared with an [illegible] and the mortality, [illegible], Com- [illegible] may be stopped when the temperature has remained normal for seventy-two hours.

Tickbite Fever

Aureomycin has been shown to be therapeutic in tickbite fever.[20,21] Though the disease is usually mild, with a low mortality, the duration of illness is probably shortened; the temperature returns to normal in about three days. Three days' treatment is thought to be adequate.

Rickettsial Pox

Aureomycin is somewhat more potent than chloramphenicol and of similar potency *to terramycin in experimental infections.*[22] As few treated cases have been reported and as the disease is

naturally short-lived, assessment of their relative values cannot be made at the present time. With aureomycin and terramycin, symptomatic improvement and fall of temperature take place within twenty-four hours.[22,23] Three or four days of antibiotic therapy appear to be sufficient.

Q Fever

Aureomycin is recommended for the treatment of Q fever,[24] though it appears that chloramphenicol is only slightly less active.[25,5,11]

When full doses are employed a successful response is usual, but [illegible]

least three days.

Psittacosis

Penicillin, in high concentration, is active against the virus of psittacosis[27] and is curative in a few patients suffering from this disease Aureomycin, however, has been shown to be superior and should be employed.[24] With this antibiotic toxæmia and fever rapidly subside, often within forty-eight hours; relapses on omission of treatment have, however, been reported.[25] The minimal safe duration of treatment is probably at least five days The effect on the mortality rate (previously about 30 per cent) has not been determined

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Chapter XVII

VENEREAL DISEASES

Gonorrhœa

CAUSATIVE ORGANISM. *Neisseria gonorrhœæ*

DRUGS OF CHOICE AND DOSES

Uncomplicated urethritis.

(1) **Procaine penicillin** in arachis oil with 2 per cent. aluminium monostearate. 300,000 units, one injection; intramuscular.

(If aqueous procaine penicillin is used two doses must be given)

muscular.

(2) **Streptomycin:** 1 gm. for three days; intramuscular.

Metastatic Complications:

(1) **Procaine penicillin:** 600,000 units for eight days; intramuscular.

(2) **Fever therapy.**

CHOICE OF DRUG.—Penicillin is the most effective antibiotic, but has the disadvantage of masking early syphilis This can be overcome by giving the minimal therapeutic dose as recommended above, or alternatively by employing streptomycin, which has little action against spirochætes[1] Whenever penicillin is used the Wassermann and Kahn reactions must be performed after three weeks, three

mended for routine use on the grounds of expense and because they have not been shown to be superior to penicillin or strepto-

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Chapter XVII

VENEREAL DISEASES

Gonorrhœa

CAUSATIVE ORGANISM: *Neisseria gonorrhœæ*

DRUGS OF CHOICE AND DOSES

Uncomplicated urethritis:

(1) **Procaine penicillin** in arachis oil with 2 per cent aluminium monostearate. 300,000 units, one injection; intramuscular.

(If aqueous procaine penicillin is used two doses must be given.)

(2) **Streptomycin:** 1 gm. one injection; intramuscular

Relapses: twice the above dosage should be given.

Local Complications:

(1) **Procaine penicillin:** 300,000 units for three days; intramuscular.

(2) **Streptomycin:** 1 gm. for three days, intramuscular.

Metastatic Complications:

(1) **Procaine penicillin:** 600,000 units for eight days, intramuscular.

(2) **Fever therapy.**

CHOICE OF DRUG.—Penicillin is the most effective antibiotic, but has the disadvantage of masking early syphilis This can be overcome by giving the minimal therapeutic dose as recommended above, or alternatively by employing streptomycin, which has little action against spirochætes[1] Whenever penicillin is used the Wassermann and Kahn reactions must be performed after three

[1] [illegible]

they have not been shown to be superior to penicillin or strepto-

with arsenicals can be determined and final recommendations be made.

CRITERIA OF CURE.—Treatment should be directed principally to the healing of lesions and relief of symptoms. Negative serological reactions are often not obtainable, and no benefit results from continuing treatment indefinitely after the infection has been clinically arrested.

RESULTS OF TREATMENT.—The extent to which a lesion can be healed depends largely upon the amount of fibrosis and irrever- [illegible]

Congenital Syphilis

PROPHYLAXIS (TREATMENT OF THE MOTHER)

A course of penicillin, as recommended for early acquired syphilis, should be given if possible before the third month of pregnancy to all women, even though they may already have been adequately treated Those who have received no previous treatment [illegible] weekly for [illegible] ate in pregnancy, are excellent. In only about 1 per cent. will the infant be affected.[5]

TREATMENT (TREATMENT OF THE CHILD)

Penicillin: 1,500 units per pound of body weight four-hourly for twelve days; intramuscular.

Bis[illegible] of body weight (increasing as [illegible]

CHOICE OF DRUGS.—Penicillin alone is highly effective in nearly all infants, except those who are marasmic owing to the extent and severity of the disease. It is advisable to give penicillin to all [illegible] if there is doubt [illegible] disease progresses in spite of bismuth and penicillin, it is recommended that arsenotherapy should be routinely used. Late manifestations, such as interstitial keratitis, juvenile paresis and Clutton's joints, often show little clinical or serological improvement.

SPECIAL CONSIDERATIONS

(1) **Interstitial keratitis.**—See page 146.

(2) **General Treatment.**—Nutrition and local conditions, such as snuffles, must in all cases receive careful attention.[6]

CRITERIA OF CURE.—Absence of clinical or radiological lesions with negative Wassermann and Kahn reactions at the end of five years' observation may be taken as evidence of cure. Nevertheless, periodic examinations should be made subsequently except in mild cases diagnosed and treated in early infancy.

Bacterial Urethritis (Non-gonococcal)

The following organisms may be responsible for urethritis, and the appropriate drugs are stated in each instance in order of preference.[7]

(1) *Staph. aureus* (page 100.)	(1) Penicillin.
	(2) Aureomycin.
(2) *Str. fæcalis* (page 100)	(1) Mandelic acid.
	(2) Aureomycin.
	(3) Penicillin and streptomycin
(3) *Bact. coli* (page 98)	(1) Sulphonamides.
	(2) Chloramphenicol.
	(3) Sulphonamides + streptomycin.
(4) *Staph albus*	(1) Penicillin
	(2) Mandelic acid.
	(3) Aureomycin
(5) *Proteus vulgaris* (page 99.)	(1) Streptomycin
	(2) Alkalies
(6) *Ps. pyocyanea* (page 99)	(1) Polymyxin
	(2) Streptomycin.
(7) *Bact. friedländeri*	(1) Streptomycin.
	(2) Aureomycin

(*Modified from Dr. A. H. Harkness*)

Abacterial Urethritis

CAUSATIVE ORGANISMS

The condition is probably not a single disease entity; one type is associated with a pleuropneumonia-like organism and another with inclusion bodies.

K

DRUGS OF CHOICE

(1) oral.
(2)
(3)

CHOICE OF DRUG AND RESULTS OF TREATMENT.—Aureomycin appears to be more successful than streptomycin, especially when there are metastatic complications. Fever therapy may also be employed for the latter. Sulphonamides are less effective, but are sufficiently active to justify their use in uncomplicated urethritis.

Soft Sore

CAUSATIVE ORGANISM: *Hæmophilus ducreyi*

DRUGS OF CHOICE AND DOSES

(1) **Sulphathiazole, "Sulphatriad":** 1 gm. four-hourly for five

(2)

C

chloramphenicol

he

c-

tion with streptomycin for the treatment of buboes. If suppuration is present aspiration is often necessary and the response to antibiotics is less favourable.

Lymphogranuloma Inguinale

CAUSATIVE ORGANISM: Virus

DRUGS OF CHOICE AND DOSES

(1) **Aureomycin:** 500 mg. six-hourly; oral.
(2)
(3)

chloramphenicol is uncertain, but probably longer than ten days.)

CHOICE OF DRUG AND RESULTS OF TREATMENT.—Aureomycin, chloramphenicol and streptomycin are more effective than antimonials and sulphonamides. Streptomycin is preferred to the newer antibiotics, because it is given by injection and there is no

doubt that the full dosage has been administered. Suppuration, for which aspiration will be required, and proctitis affect the response adversely.

Granuloma Venereum

CAUSATIVE ORGANISM: *Calyminatobacterium donovani*

DRUGS OF CHOICE AND DOSES

Aureomycin or chloramphenicol, in the same doses as for lymphogranuloma inguinale, are the most effective remedies. Penicillin is of value in controlling secondary infection due to sensitive bacteria.

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Chapter XVIII

INFECTIONS OF THE SKIN

In the treatment of infections of the skin there are important factors which influence the action of antibiotics and impose limitations on their use. Functional and anatomical disturbances, such as eczematisation, seborrhœa and fibrosis, impair the skin's natural ability to heal and predispose to relapse after infection. Certain metabolic disturbances—for instance, debility, vitamin deficiency and diabetes mellitus—may be ætiological and similarly, unless corrected, render permanent cure improbable.

When infection has been controlled permanent cure may be achieved if secondary changes in the skin are minimal and resolve spontaneously. Usually, however, they have reached a stage where spontaneous resolution does not take place, and lasting benefit depends more upon other methods of treatment than upon antibiotics.

The frequency and severity of sensitisation dermatoses is

exfoliative type, are often more intractable than the primary condition, and may be so severe that life itself is endangered. At

reason most dermatologists deprecate the local use of penicillin. If there is no alternative and penicillin must be used, the closest supervision is imperative and courses must be of short duration. Fortuitous contact with penicillin, such as may occur in patient, nurse or doctor during the injection of penicillin, is a potent cause of sensitisation; attention to the technique of injection is the best means of prevention. It should be remembered that sensitisation occurs more readily in those who have an allergic tendency than in normal persons.

There is a growing volume of evidence to support the view that cross-sensitisation between generically related antibiotics and fungi

es place—*e.g.*, penicillin may act as a sensitising agent to aureo-

erapy.

In dermatology sulphonamides, penicillin, streptomycin, chlor-
phenicol and aureomycin should be administered systemically.
r the reasons already given, and on account of the relatively low
ncentrations obtained at the site of infection in the skin, the

The value of aureomycin, terramycin and chloramphenicol in
e treatment of other diseases caused by viruses is on the whole
sappointing, though improvement has been reported in many
dividual cases [1]

Before instituting antibiotic therapy, the physician must be
tisfied that there is little risk from sensitisation reactions, that the
fecting organism is sensitive to the chosen agent, and that the
sease is of a type known to respond. If these conditions are
lfilled it still remains to employ to the full other local or general
ethods of treatment, in accordance with the general principles of
ermatology.

The status of the newer antibiotics, their relative therapeutic
lues and optimal régimes are to a large extent undecided As
perience increases, there is little doubt, however, that there will
e modifications of present views and treatment

OSES—SYSTEMIC ADMINISTRATION (ADULTS)[2]

intramuscular.

For lupus vulgaris 1 gm. daily for at least six weeks, intramuscular, in conjunction with calciferol 300,000 units weekly.

TOPICAL APPLICATION

Tyrothricin: 1 in 1,000 solution or w/w in an ointment base.
Bacitracin: Expensive and not available in this country.

CHOICE OF DRUG.—In the following table are given the preferred *antibiotics in order of therapeutic value. In the majority of* diseases non-specific measures are also necessary and may be more important than antibiotics.

Bacterial Infections

DISEASE	ORGANISM	ANTIBIOTIC
1. Boils Carbuncles	Staphylococci	(1) Tyrothricin (local) (2) Penicillin (intramuscular) (3) Aureomycin (oral)
2. Eczema, infected Folliculitis	Staphylococci Streptococci	As above
3. Impetigo Pyodermias	Streptococci Staphylococci	(1) Non-specific measures: (i) Hydrogen peroxide, potassium permanganate (ii) Ung. hydrarg. ammon. dil. (iii) Vioform, etc. (2) Antibiotics as above
4. *Intertrigo*	*Staphylococci* Streptococci	*(1) ½ per cent. silver nitrate* (2) Antibiotics as above
5. Sycosis barbæ	Staphylococci	(1) Tyrothricin lotion (local) (2) Penicillin (intramuscular) (3) Aureomycin (oral) (4) Streptomycin (intramuscular) (with "Quinolor" to beard area)
6. Erysipelas	*Strep. pyogenes*	(1) Penicillin (intramuscular) (2) Sulphonamides (oral)

7. Pemphigus neonatorum	*Staph. aureus*	(1) Penicillin (intramuscular) (2) Aureomycin (oral)
8. Lupus vulgaris	*Myc. tuberculosis*	(1) Calciferol (2) Calciferol + streptomycin
9. Anthrax	*B. anthracis*	(1) Penicillin + Sclavo's serum (2) Arsenicals
10. Swine erysipelas	*Erysipelothrix rhusiopathiæ*	(1) Penicillin + sulphonamides (systemic)
11. Diphtheria	*C. diphtheriæ*	(1) Antitoxin (2) Penicillin (systemic)
12 Tularæmia (primary)	*Br. tularense*	Streptomycin
13. Cutaneous leishmaniasis		No effective antibiotic

Virus Infections

1. Herpes febrilis	(1) Antihistaminics (limit damage) (2) Antibiotics (limit secondary infection)
2. Herpes zoster	As above
3. Lymphogranuloma inguinale	(1) Aureomycin (2) Chloramphenicol (3) Penicillin (4) Streptomycin

Diseases of Unknown Origin

Bullous Eruptions

1. Dermatitis herpetiformis ..	(1) Sulphapyridine (systemic) (2) Aureomycin (oral) (control but do not cure)
2. Pemphigus vulgaris 3 Pemphigus foliaceus	Cortisone
4. Bullous erythema multiforme (Stevens-Johnson syndrome)	(1) Aureomycin (oral) (2) Chloramphenicol (oral) (control blister formation)

Fungus Infections

1. Monilia	Aggravated by antibiotics (1) Gentian violet (2) Sulphonamides
2. Epidermophyton	Aggravated by antibiotics derived from moulds
3. Trichophyton, Microsporon	(1) X-ray epilation (2) Mercurials (3) Tyrothricin (4) Systemic penicillin or aureomycin for secondary infection

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Chapter XIX

INFECTIONS OF THE EYE

General Considerations

THE inflammatory reaction of the eye to the presence of pathogenic bacteria, viruses and other injurious substances is in certain conditions, such as uveitis, complicated by tissue hypersensitivity.

Simple inflammatory reaction subsides when the causal organism is removed, whereas reaction due to hypersensitivity persists. Thus, lesions characterised by inflammation respond to antibacterial or antiviral agents more favourably than do those which are due predominantly to hypersensitivity

Accurate clinical diagnosis is therefore an essential step in differentiating suitable and unsuitable cases, and in all those for which antibiotic therapy is indicated the bacteriological diagnosis must also be made, for upon this rests the choice of antibiotic.

The structure of the eye imposes further limitations on the use of antibiotics and determines the routes by which they are administered to secure a therapeutic effect The vascular tissues of the eye are similar to vascular tissues elsewhere, in that adequate local concentrations of antibiotics can be obtained after systemic administration; however into the avascular structures (cornea, aqueous and vitreous) penicillin, streptomycin, aureomycin and chloramphenicol in normal doses, diffuse in negligible quantities. They must therefore be applied locally by subconjunctival or retrobulbar injection. Massive systemic doses (2,000,000 units) of penicillin are sufficient to give therapeutic concentrations within the eye and are usefully employed in certain lesions—*e g.*, interstitial keratitis. The more soluble sulphonamides, such as sulphacetamide, diffuse more readily into the aqueous, in which the concentration approaches two-thirds of that in the plasma and persists for longer time; but the greater potency and wider range of penicillin and the newer antibiotics have limited the number of conditions for which sulphonamides are preferred

Infection of the eye causes damage to the tissues which may become irreparable within a few hours of onset. Even after minor

injury the tissues are slow to heal and regain their functional integrity.

In apparently trivial infections prompt institution of effective treatment is therefore essential, and at the earliest sign of intraocular spread it becomes a matter of the greatest urgency.

The status of the newer antibiotics—streptomycin, aureomycin, chloramphenicol and polymyxin—is not fully established. Streptomycin and aureomycin have been most widely tried, and have been found especially valuable for the treatment of infections by penicillin-insensitive organisms.

Favourable results have been obtained with streptomycin in infections due to *Ps. pyocyanea*, sensitive Gram-negative bacilli and the tubercle bacillus. It appears to be beneficial in phlyctenular *conjunctivitis. Aureomycin has been successfully employed in* infections due to penicillin-resistant staphylococci and in mucopurulent conjunctivitis of infancy.[4]

For further description of preparations, doses and techniques of administration of these antibiotics the reader should consult the original reports.

Undoubtedly antibiotics have brought a great advance in the treatment of ocular infections, but they have in no way diminished the need for ancillary treatment when the accepted indications are present.[1]

Ophthalmia Neonatorum

Causative Organism: *Neisseria gonorrhœæ*

Drug of Choice

[illegible] ml).

1 drop every thirty minutes for three hours.
1 drop every hour for six hours.
1 drop every two hours for six hours.[2]
(To be repeated if necessary.)

Choice of Drug.—Sulphonamides (oral) are not uniformly effective as so many infections are due to resistant organisms. Penicillin (local) should therefore be relied upon and employed from the outset.

Special Considerations

(1) **Prophylaxis.**—One drop of 20 per cent. argyrol should be

instilled into each eye if the maternal genital passages are unhealthy. As argyrol is irritant it is seldom employed for routine prophylaxis

(2) **Preparatory Cleansing of the Eye.**—Penicillin instillation must be preceded by cleansing of the eyes with saline If there is corneal haziness, atropine sulphate (1 per cent.) should be instilled. (The operator must be careful to avoid infection from pus ejected under pressure when he separates the lids.)

(3) **Swabs for bacteriological culture** must be taken in all cases before treatment is started.

RESULTS OF TREATMENT.—With prompt treatment most cases are cured by a single course, but a few will require re-treatment. Minor degrees of corneal haziness may be expected to clear Failure of treatment is most frequently due to the presence of insensitive organisms or to delay in instituting treatment.

Purulent Conjunctivitis

CAUSATIVE ORGANISMS *Staphylococcus aureus*
Pneumococci
Staphylococcus albus
Streptococci

DRUGS OF CHOICE

(1) **Crystalline Penicillin:** Local instillation régime as for ophthalmia neonatorum
(2) **Aureomycin Borate:** 0·5 per cent. solution, local instillation régime as for penicillin

SPECIAL CONSIDERATIONS

Bacteriology.—Swabs must be taken before the start of treatment to determine the organism. If this is a staphylococcus its sensitivity to penicillin must be estimated. Higher concentrations of penicillin may be sufficient to control partially insensitive organisms, but aureomycin should be used for those which are highly resistant.

Mucopurulent Conjunctivitis, Blepharitis

In mild cases irrigation of the eyes with normal saline and cleansing the lid margins is often adequate. Penicillin (2,500 units per ml) is only necessary in the more severe infective cases.

The treatment of predisposing conditions such as seborrhœa or nasal sepsis, which favour relapse and chronic infection, is

essential and is frequently of more value than the application of antibiotics. Blepharitis, associated with conjunctivitis, resolves when the latter is treated. In chronic blepharitis penicillin ointment (1,000 units per gm.) should be applied three times daily for at least two weeks. Absence of response within this period implies that penicillin is without effect. Good results have also followed the use of aureomycin.

Dacryocystitis

[illegible]
lo[illegible]
ne[illegible]
the organism is sensitive, but being of limited range and less effective in the presence of pus, is not preferred.

Styes

For the treatment of recurrent styes, general measures are *beneficial and should be fully utilised. Penicillin ointment (1,000* units per gm.) three times daily helps temporarily to control infection.

Trachoma

CAUSATIVE ORGANISM: Virus
Secondary bacterial invaders

DRUGS OF CHOICE

(1) **Aureomycin Borate:** 0·5 per cent. drops, local.
(2) **Chloramphenicol.**
(3) **Penicillin.**

CHOICE OF DRUG.—Aureomycin is the most effective antibiotic available and is thought to be superior to chloramphenicol. It is probable that the response is due to the action in controlling secondary infection, rather than to any effect on the virus. Penicillin and sulphonamides may also be useful by controlling bacterial infection.

RESULTS OF TREATMENT.—Even advanced lesions have been found to clear following local aureomycin therapy, though pannus

of variable extent nearly always remains and histological cure has not been recorded The number of patients treated is too small to permit any final conclusions as to the effect or optimal régime of treatment.

Infected Corneal Ulcer and Hypopyon

ORGANISMS. Staphylococci, pneumococci, diphtheroids, *Pseudomonas pyocyanea*, etc

DRUGS OF CHOICE AND DOSES

(1) **Crystalline Penicillin:** 1,000,000 units in 0·5 ml water with 0 5 ml. of 1 in 1,000 adrenalin, subconjunctival, daily or on alternate days, for two to four days (according to severity); followed by:

Penicillin ointment, 1,000,000 units per gm., locally, every [illegible] for three days.[2] [illegible]

SPECIAL CONSIDERATIONS

(1) **Bacteriology.**—Before the start of treatment a swab must be taken for bacteriological examination and estimation of bacterial sensitivity to penicillin. If no clinical improvement is apparent within forty-eight hours, the organism may be assumed to be penicillin-insensitive and treatment must be reviewed Streptomycin may be used alone or combined with penicillin, when sensitive organisms such as *Bact. coli* are present. Sulphacetamide, tyrothricin and aureomycin may also be of value against penicillin-insensitive organisms

(2) **Atropine.**—Throughout treatment the pupil must be kept dilated by instillation of 1 per cent. atropine drops twice daily.

(3) **Reaction to Drugs.**—Watch for signs of local reaction to antibiotics must be kept.

RESULTS OF TREATMENT.—Improvement usually starts after the first injection, and corneal infiltration and hypopyon resolve in three to four days.

In most cases, especially those due to pneumococci and those in which the organism is penicillin-sensitive, complete cure may be expected.[1]

Interstitial Keratitis

CAUSATIVE ORGANISM: *Treponema pallidum*

DRUG OF CHOICE AND DOSES

P[illegible]

C[illegible]

0·5 ml. of 1 in 1,000 adrenalin, subconjunctival, on alternate days.[2]

SPECIAL CONSIDERATIONS AND RESULTS OF TREATMENT

Prompt treatment in the first attack is reported to give good visual results. In late cases there may be little or no benefit.[3] For those in which acute inflammation and corneal infiltration do not respond promptly, arsenic, bismuth or malarial therapy has been recommended.[3]

Syphilitic Iritis

Intramuscular penicillin, employed in early syphilis, causes improvement within ten days.[4] The results are more favourable than those obtained in interstitial keratitis by intensive therapy.

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Chapter XX

INFECTIOUS DISEASES

Diphtheria

CAUSATIVE ORGANISM: *Corynebacterium diphtheriæ*

DRUGS OF CHOICE

(1) **Diphtheria antitoxic serum:**
   For nasal lesions: 10,000 units; intramuscular.
   For tonsillar lesions: 20,000 to 40,000 units; intramuscular.
   For nasopharyngeal lesions: 60,000 to 100,000 units; intramuscular.
   For laryngeal lesions: 20,000 units; intramuscular.
   For multiple lesions. 40,000 to 100,000 units Intravenous or intramuscular, according to urgency.
   For severe toxæmic infections: 80,000 units[1] (40,000 units intravenous and 40,000 units intramuscular).

(2) **Procaine Penicillin:** 300,000 units daily for six days; intramuscular.

CHOICE OF DRUGS —Prompt administration of antitoxin remains the [illegible]

[illegible] such as streptococci, and is especially valuable for the prevention of secondary infection after tracheotomy. For the treatment of carriers a ten-day course of penicillin should be employed. If the organism persists a second course is often successful. Tonsillectomy is indicated where penicillin therapy has failed.

SPECIAL CONSIDERATIONS

The accepted principles of treatment and nursing of patients suffering from diphtheria must be applied.

CRITERIA OF CURE.—Two consecutive negative swabs, at an interval of one week, may be taken as evidence of freedom from infection. The duration of rest and convalescence must be decided on clinical grounds, taking into consideration the presence or absence of [illegible]

[illegible] given the majority of patients become non-infective by the ninth day.[2]

Measles

CAUSATIVE ORGANISM: Virus

SECONDARY INVADERS: Streptococci, pneumococci, staphylococci.

DRUGS OF CHOICE AND DOSES

(1) **Sulphadimidine.** Dose (for 2- to 5-year-old children): Loading 2 gm., maintenance 1 gm. six-hourly for at least five days; oral.
    (For further details see page 21.)
(2) **Penicillin.** Dose (for 3- to 7-year-old children): Loading 60,000 units, maintenance 30,000 units four-hourly for at least five days; intramuscular.
    (For further details see page 34.)

and bronchopneumonia. Measles antisera and immune gamma globulin are without therapeutic effect.

SPECIAL CONSIDERATIONS

The sole effect of antibiotics in measles is against secondary invaders. In mild cases it is safe to withhold antibiotics, but in all severe cases and where bacterial cross-infection is possible they should be employed routinely in therapeutic dosage.

RESULTS OF TREATMENT.—The prompt administration of sulphonamides has resulted in a reduction of serious complications, particularly of bronchitis and bronchopneumonia.[8] The prognosis of established complications has likewise been improved.

Relapsing Fever

CAUSATIVE ORGANISM: *Treponema recurrentis*

DRUGS OF CHOICE AND DOSES

(1) **Neoarsphenamine** (adult dose): 0·3 to 0·6 gm. in 5 ml. of water, intravenous (one injection, repeated if relapse occurs).
(2) **Penicillin** (adult dose): Loading 100,000 units, maintenance 50,000 units four-hourly, intramuscular, for two or three days.

CHOICE OF DRUG.—The efficacy of neoarsphenamine and penicillin is of the same order and both are rapidly therapeutic; penicillin is preferred when jaundice is present, as there is no risk of further injury to the liver. Aureomycin is active against the spirochæte, but

at the present time its value in the treatment of the human disease is not established.

SPECIAL CONSIDERATION

Attention to the details of general management, as in typhoid fever, remains of great importance, irrespective of the type of antibiotic therapy employed.

RESULTS OF TREATMENT.—In the great majority of patients the temperature subsides within forty-eight hours and relapses are prevented.

Virus Influenza

CAUSATIVE ORGANISM: Virus of influenza

SECONDARY INVADERS: Streptococci, pneumococci, staphylococci, *H. influenzæ*.

CHOICE OF DRUG.—It is doubtful whether the newer antibiotics exert any action against the viruses of influenza. Their beneficial effect on the human disease depends primarily on their ability to control secondary bacterial invasion. For this purpose penicillin should be employed, though aureomycin and terramycin possess possible advantages due to their wider range of activity. In all cases it is important that the choice of antibiotic be guided by the bacteriology. (For further details see Chapter X, Pulmonary Diseases, page 68.)

Virus Diseases unaffected by Available Antibiotics

1. Anterior poliomyelitis and polioencephalitis.
2. Mumps.
3. Glandular fever.
4. Chickenpox (secondary bacterial infection is controlled).
5. Smallpox (secondary bacterial infection is controlled).
6. Measles (secondary bacterial infection is controlled).
7. German measles.
8. Infective hepatitis.

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lesions is relatively poor, especially in the presence of large caseous foci and necrosis. Provided that the organism remains sensitive during treatment, it is capable of preventing further extension of the disease. Owing to the risk of emergence of streptomycin-resistant strains, *para-aminosalicylic acid (or one of the sulphones)* must invariably be administered to patients under treatment with streptomycin.[4]

(2) **Para-aminosalicylic acid**

Para-aminosalicylic acid and its salts possess a small but definite action on the tubercle bacillus. They are employed with streptomycin to delay the onset of resistance,[4] and to enhance its therapeutic effect. Alone, they are employed in patients for whom streptomycin is contraindicated, since in addition to their own antitubercular activity they reduce fever and "toxæmia," which induces a sense of well-being in the patient.[5]

[illegible]

ment of less acute human infections[6] Like para-aminosalicylic acid, they are also reported to delay the emergence of resistant strains and enhance the effect of streptomycin.[7,8,9] Since they can be given for long periods, they would appear to have a place in after-treatment as a prophylactic against delayed relapse, such as may occur in tuberculous meningitis.[10]

(4) **Thiosemicarbazones** (see page 26)

The thiosemicarbazones are believed to have a similar degree of activity to para-aminosalicylic acid. Their therapeutic value appears to be greatest in mucous membrane and intestinal tuberculosis. Like the sulphones and para-aminosalicylic acid, their effect in pulmonary tuberculosis is difficult to assess.[11]

Tuberculous Meningitis

Streptomycin, by intramuscular and intrathecal injection, must be commenced as soon as the diagnosis is made, even though confirmation by finding the organism in stained films of the cerebrospinal fluid is lacking. Treatment must be continued until the patient is gaining weight and is mentally alert and active (unless irreversible neurological damage has been suffered) The sugar concentration should be normal and the diurnal variation in the cell count in the cerebrospinal fluid small. The duration of intrathecal treatment should be at least two months even under favourable circumstances, and will usually be longer. Intramuscular

treatment should be continued for at least three months,[12] since shorter courses are more frequently followed by relapse. When improvement is apparent, injections should be given on alternate days in order to postpone the onset of eighth nerve damage. After-treatment with sulphones or para-aminosalicylic acid should be continued for a further six to nine months.[10] The mortality of [illegible]

Miliary Tuberculosis

Intramuscular streptomycin therapy should be given for four months or longer, depending on the radiological appearances, weight gain, general condition and sedimentation rate. Lumbar puncture should be performed weekly to detect pre-clinical meningitis

In cases uncomplicated by meningitis the mortality rate is about 50 per cent. at the end of one year.[13]

Acute Tuberculous Bronchopneumonia

Intramuscular streptomycin therapy will be required for not less than three months. In favourable cases, longer courses of six months or more may be necessary to bring about sufficient control to allow the lung to be collapsed.

Progressive Pulmonary Tuberculosis in Adults

By virtue of its capacity to limit extension of caseating lesions and to arrest and facilitate healing in early exudative lesions, streptomycin is of great value, especially when employed in conjunction with established methods of treatment. Many lesions, which previously would have been too acute, may now be suffi- [illegible]

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(3) Sulphones (see page 20)

*The sulphones have a small but definite action against tubercle bacilli (see page 20), and are thought to be beneficial in the treat*ment of less acute human infections.[6] Like para-aminosalicylic acid, they are also reported to delay the emergence of resistant *strains and enhance the effect of streptomycin.*[7,8,9] *Since they* can be given for long periods, they would appear to have a place in after-treatment as a prophylactic against delayed relapse, such as may occur in tuberculous meningitis.[10]

(4) [illegible]

[illegible]

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months' duration may be given.

Chemotherapy has brought lobectomy within the field of safe and practicable surgery for the radical treatment of certain localised lesions.

Para-aminosalicylic acid (sodium salt) is reported to cause marked radiological improvement in 22 per cent. of patients, whereas streptomycin causes improvement in 56 per cent., the improvement being more pronounced in febrile patients. Combined therapy, owing probably to the lower incidence of resistant organisms, appears to be more effective in rendering the sputum [illegible]

improvement. Subsequent deterioration while under treatment is usually due to the emergence of streptomycin-resistant organisms and is thus less commonly encountered with combined therapy.

Advanced Chronic Pulmonary Tuberculosis

In few patients suffering from long standing pulmonary tuberculosis is the administration of streptomycin of sufficient value in treatment to outweigh its attendant risks. The large bacterial population in *individual foci reduces its efficacy and, as in many* other chronic infections, cavitation and fibrosis, more than the organism itself, determine the course of the disease and its response to treatment.

[illegible] virtually impossible, there is [illegible]

mycin.

It is advisable to restrict the use of streptomycin to those patients in whom there are specific indications, such as laryngitis.

Primary Tuberculosis

[illegible] in primary [illegible]

and puberty. On account of the character of the lesion and the presence of glandular caseation, an optimal effect from streptomycin is not to be expected.[14] For these reasons it is advisable to administer the antibiotic only to those children in whom extension [illegible] diet and to

Laryngeal and Endobronchial Tuberculosis

Tuberculous ulceration of the larynx or bronchi, which are commonly associated with pulmonary disease, must be considered, from the point of view of antibiotic therapy, as parts of the disease as a whole, rather than as separate disease entities Laryngitis, complicating advanced pulmonary disease which is beyond hope of benefit from streptomycin, may be treated solely with the object of bringing symptomatic relief, by short courses (*e.g.*, three to four weeks) of intramuscular streptomycin. A fortnight's course of inhalations of a solution containing 50 mg. of streptomycin in 1 c.c of water, every two hours, is often beneficial. When systemic streptomycin is employed as part of a therapeutic régime, treatment should be continued for at least two months. Laryngeal ulcers are reported to heal or improve in 81 per cent and tuberculous ulcers of the trachea and bronchi in 89 per cent. of patients in a period of three months [13]

Tuberculosis of the Urinary Tract

The natural chronicity of renal tuberculosis, and the presence of gross caseation, adversely affect the action of streptomycin and thus limit its therapeutic usefulness. Treatment consists primarily of general measures in accordance with accepted principles, maintenance of an alkaline urine, and, whenever possible, radical surgery. A three to four months' course of streptomycin is recommended as an adjunct to surgery or, in inoperable cases solely for its palliative effect. Symptomatic improvement is reported in 90 per cent. of patients; the cystoscopic and pyelographic appearances improve in 80 per cent. and 25 per cent. of patients respectively. Eradication of the organism from the urine may be expected in 55 to 80 per cent. of patients, depending on the dosage and duration of treatment, but about 20 per cent. of these later have bacteriological relapse [13]

Skeletal Tuberculosis

In adults the efficacy of [illegible]

[illegible] form the basis of management. Streptomycin is particularly beneficial when sinuses are present. To obtain the greatest benefit it is probably necessary that specific therapy should be continued for three months or longer.

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Since eradication of the organism is virtually impossible, there is the probability that resistant strains will emerge. Not only, therefore, will treatment fail, but in contact cases the organism may be the cause of a disease which is primarily insusceptible to streptomycin

It is advisable to restrict the use of streptomycin to those patients in whom there are specific indications, such as laryngitis.

Primary Tuberculosis

[illegible] therapy in primary

and puberty. On account of the character of the lesion and the presence of glandular caseation, an optimal effect from streptomycin is not to be expected.[14] For these reasons it is advisable to administer the antibiotic only to those children in whom extension of the disease continues in spite of adequate rest and diet, and to children under the age of two years, for whom, if untreated, the risk of generalised spread and a fatal outcome is high.

Laryngeal and Endobronchial Tuberculosis

Tuberculous ulceration of the larynx or bronchi, which are commonly associated with pulmonary disease, must be considered, from the point of view of antibiotic therapy, as parts of the disease as a whole, rather than as separate disease entities. Laryngitis, complicating advanced pulmonary disease which is beyond hope of benefit from streptomycin, may be treated solely with the object of bringing symptomatic relief, by short courses (*e g*, three to four weeks) of intramuscular streptomycin A fortnight's course of inhalations of a solution containing 50 mg of streptomycin in 1 c.c. of water, every two hours, is often beneficial. When systemic streptomycin is employed as part of a therapeutic régime, treatment should be continued for at least two months Laryngeal ulcers are reported to heal or improve in 81 per cent and tuberculous ulcers of the trachea and bronchi in 89 per cent of patients in a period of three months [13]

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Tuberculous Lymphadenitis and Cold Abscesses

Since the predominant feature of tuberculous cold abscesses is caseation, streptomycin is of little or no therapeutic value, except when drainage is established by surgery or through sinuses or fistulæ. Many cases of cervical adenitis may be treated successfully by incision and expression of the caseous material, thus reducing the need for block dissection. Streptomycin therapy should be instituted at least ten days before operation and continued for two to three months. Local injection is a promising method of augmenting the effect of systemic streptomycin. Local injection of PAS is also employed, though its value has not been finally established.

Secondary Intestinal Tuberculosis

Para-aminosalicylic acid is recommended for the treatment of secondary intestinal tuberculosis.[15] Streptomycin is also highly effective, but is not advisable for routine use, since as a rule the disease is a complication of advanced pulmonary tuberculosis.

Tuberculous Peritonitis

In tuberculous peritonitis which has a tendency to spontaneous [illegible] employed [illegible] ought to be employed.

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Chapter XXII

TROPICAL DISEASES

Cholera

CAUSATIVE ORGANISM *Vibrio choleræ*

DRUGS OF CHOICE

Sulphaguanidine (adult dose): Loading 4 gm, maintenance

possessing a rapid action, be free from toxic effects,[1] especially on the kidneys. Nevertheless, early trials with chloramphenicol, which fulfils these requirements, have not been encouraging.

SPECIAL CONSIDERATIONS

(1) **Correction of Dehydration, Electrolyte and Colloid Loss.**—Restoration of fluid, salt and protein by intravenous infusion is the most important part of treatment, and at the present time is the only method which lowers the mortality

(2) Drug Toxicity.— [illegible]

(3) **Limitations of Chemotherapy.**—The continued presence of vibrios after the onset of symptoms does not render the death rate higher than in those whose stools become negative. This occurs just as rapidly without the use of vibriocidal drugs as when they have been used. In about 85 per cent of patients[1] death is due to peripheral circulatory failure or uræmia, for which correction and maintenance of fluid and electrolyte balance are indispensable and specific. Thus, vibriocidal drugs may only be expected to be beneficial if they are given at an early stage before the disease has become established[2]

CRITERIA OF CURE.—Once clinical recovery has set in, further

hydnocarpus treatment with orthopædic surgery and physiotherapy.[8]

The majority of patients suffering from leprosy on DADPS show clinical and bacteriological improvement (72 per cent. and 62 per cent. respectively).[7] Results of treatment by other compounds are thought to be similar, though sulphetrone may be slightly superior.[5,6] Relapses occur with great frequency (45 per

alternative therapy, and the results of long-term follow-up, are necessary to determine the final therapeutic value and limitations of the sulphones.

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TABLE OF ANTIBIOTIC ACTIVITY

Numbers· Numbers are used to indicate the order of preference *of antibiotics* or antisera in the treatment of infections by specific organisms *They* do not necessarily indicate *in vitro* superiority.

Asterisk. An asterisk indicates that the antibiotic should be *employed in* combination with another

Brackets· Numbers *in brackets* indicate that the antibiotic possesses an antibacterial action, but is without therapeutic effect.

+ . + indicates that the antibiotic exerts a therapeutic action, *but that its* practical value has not been fully established.

? ? indicates that *therapeutic* action is doubtful.

	Aureo-mycin	*Chloram-phenicol*	*Terra-mycin*	*Strepto-mycin*	*Penicillin*	*Polymyxin*	*Sulphon-amides*	*Sulphones*	*Antisera*
ococci	1	2	+	3	1		4		
genes	2		+	3	1		2		
lactica	2				1				
alis	1			2*	2*				
dans	2			3	1		2		
-umoniae	2		+		1		2		
heriae					(2)				1
his	?				1		2		1
linum					(2)				1
ni					(2)				1
-acis	2			+	1		+		1
-allidum	2	2	+		1				
-currentis	2				1				
rtenue	2				1				
ncentis					1				
ngitidis	2			3	1		1		
rrhoeae	2	3		2	1				
lis	2	1	+	3*		1	2		
rogenes						1			
edlanders	+	+	+	2		1	3*		
vulgaris		2		1					
morgani									
yanea	3			2		1			
phi		1							
-aratyphi		1							
-teritidis		1							
olerae suis		1							
-ae		1					2		
-tera		1				+	1		

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